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PERNIO: A VASCULAR DISEASE

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THE condition referred to in this paper as "pernio" may be effectively studied and treated by considering it as a distinct vascular syndrome. In the past, the nomenclature has included many variations and stages of this disease which the investigators have classified under fifteen or more names, including chilblains,[1] erythema induratum,[2] Bazin's disease,[3, 4] erythrocyanosis,[5-7] dermatitis hiemalis,[8] l'engelure,[9] lupus pernio,[10-12] pernio,[13] Frostschaeden,[14] erythrocyanosis crurum puellaris,[15] and acrocyanosis.[16]

A review of the literature back to Bazin[3] (1858) indicates the necessity for clarifying a confused picture. In American journals the majority of the descriptions which have appeared have been written from the dermatologist's point of view.[17, 18]

REVIEW OF LITERATURE

This syndrome has been erroneously confused with the erythema induratum of Bazin in many cases reported in the literature. In Bazin's original monograph[3] there are several case reports which fit our description, but they are labeled erythema induratum. We believe that this has been in part instrumental in producing the confusion which exists in this subject, and it has led us to attempt a clarification at this time.

Bazin's erythema induratum is a tuberculide lesion[19] (the tubercle bacillus was unknown at the time he wrote, 1857). Tubercles, not merely giant cells, must be present if one is to make a diagnosis of true Bazin's disease. The presence of giant cells seems to be the criterion of some authorities in classifying cases such as ours as tuberculide, thus

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adding further to the confusion in calling pernio "erythema induratum." Actually, giant or multinucleated cells are often seen in long-standing inflammatory processes.

Translations of some of Bazin's descriptions of erythema induratum will illustrate similarities to our cases, but, in the light of present knowledge, we feel that certain of them are descriptions not of true erythema induratum, but of "pernio."

As reported in Bazin's case 1, a laundress, aged 20, was examined May 21, 1858. She had never had enlarged glands. One sister had a seropurulent eye discharge. At the age of 11 she had an abscess at the angle of the left jaw which persisted to the age of 20. Her menses were irregular, not abundant, and often stopped for three months. Six months before the examination (in November), she developed red plaques on the lower part of her right leg, and these plaques increased in size. Two months later she developed similar lesions on the left leg. There were irregular plaques, 5 to 6 cm. in diameter, on the internal malleolus, which were violaceous in color; these disappeared with pressure. Touching them gave one the impression of an induration under each plaque. There were several smaller points in addition to the main areas. There were elongated plaques on the anterior surface of the tibia which were indurated and violaceous red. On the right leg there was a large irregular plaque which was violaceous red, with some sensation of an indurated band on palpation. In addition, there were several individual areas with the same characteristics, namely, they were indurated, regular, superficial, and not painful to pressure. (Bazin felt that the above facts distinguished this from the other types of erythematous nodules.)

Bazin suggested, in 1861, that in his opinion the suppression of menstruation was significant in producing these lesions. He did not note a seasonal variation, but he reported that the illness dated from November, that the patient entered the hospital May 21, and that she left July 2. At that time the redness and induration were practically gone. None of her family had a similar condition. The lesions in this case were not painful and did not progress to ulceration, but they were in other ways quite typical of the lesions noted in pernio.

In Bazin's Case 16, he reported that the lesions appeared on the subject's hands, nose, and jaw, and that they disappeared in the summer.

In Bazin's Case 66, he reported a man, aged 20 years, with ulcers of the leg and nasal bone. (This may, or may not, fit into our classification.)

In Bazin's case 67, he reported a man, aged 27 years, who had ulcers of the internal and external malleoli of the right leg, toes, and the soles of both feet. He also had pulmonary tuberculosis and tuberculosis of the kidney. His death was caused by Bright's disease. (We mention the general pathology in this case because it raises a serious question

as to the true character of these lesions which, although they bear certain resemblances to pernio, we feel were more likely tuberculous.)

In Bazin's case 146, he described a condition of chilblains in young females, particularly laundresses. In these cases the lesions had a predilection for the external and inferior portion of the leg and the surface along the Achilles tendon. It appeared that, at times, this condition was related to scrofula, but Bazin did not establish its connection with tuberculides.

It would appear from these descriptions that Bazin was dealing with two or possibly three different conditions, calling them "scrofula," when in reality, they were probably erythema induratum, tuberculosis, and pernio. Although there are no pathologic descriptions to confirm our impression, the clinical history in these cases tends to bear this out.

In 1894, Corlett[20] described pernio, which he called "dermatitis hiemalis," in a paper which was read before the Congress of Medicine in Rome. This deserves attention because it was the first attempt to discuss many of the characteristics of this syndrome. The following is a brief synopsis of his description of the disease. It is characterized by:

(1) The sudden appearance of lesions at the first approach of cold weather;

(2) Spontaneous cure in the spring;

(3) The possibility that the condition may recur perennially for several years;

(4) A characteristic appearance of the lesions on the dorsal surface of the hands most frequently, and on the corresponding surface of the feet next in frequency;

(5) The fact that there is little or no tendency of the disease to spread to other parts of the body or to extend at the periphery after the lesions are fully developed;

(6) The fact that "the eruption is characterized by vari-sized round or, as involution proceeds, horseshoe-shaped patches which are slightly raised, sometimes markedly thickened, and which have an abrupt, well-defined margin and a dusky-red or slightly erythematous color. At first, vesicles are present and rupture, leaving denuded, weeping, irregular pin-head to lentil-sized surfaces whose color is perceptibly stronger than the surrounding patch, and may be likened to a raw ham tint. Later, the patches take on a faded rose-colored hue, and they become covered with a thin layer of adherent scales";

(7) The fact that the intensity of the violaceous color of the affected area varies with the temperature of the room and with elevation or depression of the hand;

(8) The fact that itching may or may not be present;

(9) The fact that the condition described is not associated with any other disease.

In 1896, Corlett[21] again read a paper on this disease at the Third International Congress of Dermatology. In this paper there was little new except that he reported a difference in the size of the lesions under discussion. He reported fifteen cases, all of which occurred in cold weather, showed obstinacy to treatment, and invariably disappeared with the approach of warm weather. From this evidence it is certain that he was describing a type of disease which was dependent upon the presence of cold weather. Although this condition appears to resemble in some respects winter eczema of the type recently redescribed by Niles,[22] it may easily have been a stage of development of pernio.

We believe that the confusion of the three conditions, pernio, erythrocyanosis, and the blue limb in anterior poliomyelitis, led Telford,[23] in his report of 1933, to arrive at the conclusion that Bazin's disease is no different from erythrocyanosis, that is to say, pernio. He seemed to base his conclusion on the presence of giant cells in the nodules. These, he contended, were the reason for calling the lesions tuberculous. However, no true tubercles were found. In this discussion it must be remembered that, at the time of Bazin, the tubercle bacillus had not yet been discovered, and that he did not include histologic descriptions of the lesions. The clinical histories, physical findings, and pathologic descriptions, as reported by Telford, are similar to ours.

Telford inferred that the lesions occurred only where there was an excessive deposit of fat, particularly in stout, florid people with large limbs. He held that a defective venous return, plus the excessive fat and the action of cold weather, combined to precipitate the lesions; that the clinical and histologic picture in this syndrome was identical with that of the purple limbs and chilblains of long-standing, severe poliomyelitis; that erythrocyanosis was identical with Bazin's disease; and that there was a common basis for all of these various lesions.

Eugman,[24] in 1919, described lesions almost identical to those which we will present, but he made no mention of their seasonal occurrence. He classified the lesions as tuberculides, and he spoke of their frequent occurrence in young girls working in the large shoe factories of St. Louis.

Klingmuller and Dittrich,[14] in 1926, published a study on "Frostschaeden," and stated that the vascular damage in this condition leads to perniosis. Microscopic examination of sections revealed that there was secondary damage to the tissues, resulting from the initial damage to the vessels. This damage then extended into the fat tissues and the subcutis. The variations in the clinical picture depended upon the area involved, and varied from an elephantiasis-like swelling of the extremities in the fleshy areas to frank ulcers in the areas where the skin was thin. The ulcers appeared in the fall and winter.

Nardelli,[13] in 1926, differentiated perniosis from Bazin's disease and stated definitely that the mere presence of giant cells was no reason for

classifying perniosis as a tuberculide. Rather, the presence of giant cells was evidence of cell destruction. He noted that perniosis had a seasonal occurrence, whereas true Bazin's disease did not. It was his opinion that the two conditions could coexist, but that tuberculosis was a complication rather than a cause of perniosis.

Von Norden,[25] in 1928, reviewed the literature and discussed the methods then in use for the treatment of perniosis. He reported the use of an ointment of salicylic acid, methyl ester, and oleum fali vale, or this product in conjunction with urea, for soaks or foot baths. According to von Norden, this treatment led to recovery in many instances. By recovery he meant not only the disappearance of the chilblains during the same winter, but also a reasonable assurance that the lesions would not recur the following winter.

Dittrich,[26] in 1929, attempted the correlation of the histologic changes with the clinical observations and commented on the multiform manifestations of perniosis folliculosis, due to the variations of the lesions of the follicles from slight edema to atrophy, associated with marked discoloration. He called attention to the hyperkeratosis of the follicles. No local anesthesia was used when taking the biopsies in his cases, so that changes in the skin could not be attributed to the effects of an anesthetic.

He concluded that ulcerative perniosis developed from the above histologic picture, with edema as the basic factor, and passed through the stage of bulla formation. The primary histologic defect occurred in the epithelium and the subepithelial layer. The ulcers showed the characteristics of necrosis, and tended, therefore, to mask the true lesion as described above. The area of predilection in one of his cases was the arms, and, in another, the ear; all the rest were confined to the lower portion of the legs. The ages of his patients ranged from 18 to 32 years.

Dittrich wrote as follows: "Chilblains or perniosis does not represent a 'freezing to death' of the tissues. Such severe damages are not necessary; rather, slight effects, either of repeated or chronic stimuli, are sufficient to produce this syndrome. It is not the frost, as such, but the variations in temperature which produce the stimuli. These stimuli represent a strain to the peripheral regulatory temperature mechanism, and particularly to the anatomical structures of this functional mechanism in the vessels of the skin, which are not capable of compensating properly for these demands because of a primary hereditary or acquired functional deficiency."

He preferred the name "perniosis" as an all-inclusive term, embracing all the stages of this disease. The etiology was still unknown, but it was definitely not tuberculosis. The tubercle bacillus was never found, either within frost-damaged tissue, or in guinea pig inoculations from this tissue. Of the multiplicity of precipitating factors, only one

remained constant, namely, lowering of temperature. He divided the disease into four stages similar to the classification suggested later by Buerger, and recounted below.

Dittrich's two articles are most comprehensive, and are worthy of study by all interested in this subject.

Perutz,[15] in 1929, reported eighty cases of frostbite localized at the inner aspect of the knee joints. In his series, the disease occurred in girls and women only. This form of frostbite was not mentioned in the extensive paper on frost damages by Dittrich.[26] The age, sex, and good state of nutrition caused Perutz to call it "erythrocyanosis crurum puellaris." According to his description, the dermatosis appeared alone, or in combination with erythrocyanosis crurum puellaris. The slightest form was an erythema, varying in color from bright pink to dark red. The peculiar, icy coldness of the diseased skin was characteristic. The lesion differed from erythrocyanosis in the lack of violet discoloration. He divided the disease into four stages: color change, swelling of follicles, formation of small, livid nodules like those seen in perniosis, and, lastly, ulceration of nodules.

Perutz did not call it a new disease, but thought it was related to perniosis. Had he presented histologic material, we would be in a position to comment further. As it is, it should be pointed out that the stages, as he described them, are similar and comparable to what we shall describe, and that he probably was dealing with perniosis. The predilection for the knee joints and no other portion of the legs is difficult to explain. He mentioned that some authors believed erythrocyanosis was a superficial and diffuse form of tuberculosis of the skin, or a disease which was related to tuberculosis. He investigated these phases of the subject and was unable to correlate the clinical and dermatologic features with tuberculosis. This, too, has been our experience.

The endocrinologic background which was proposed by Perutz for this syndrome was based on the assumption of a vasoparalytic frost damage, superimposed upon an endocrine dysfunction of the capillaries. Since it is difficult to present the pros and cons of this view, and since such a discussion would only add to the confusion of the subject, it seems wiser to leave this matter in its present state of flux.

Lewis,[27] in 1929, mentioned a condition similar to ours, and called it "chilblains" or "erythema pernio," ascribing it to poor peripheral circulation or an injured vosomotor mechanism.

Kreindler and Elias,[16] in 1931, described a juvenile acrocyanosis in young adults which they believed to be due to an endocrine disturbance or an imbalance in the autonomic nervous system, resulting in impaired circulation. The capillaries showed a spastic tendency, or a slowing of circulation, with dilatation of the venous branches and the venous subpapillary plexus. They stated that the reflexes of the larger vessels

were not changed, and that the disease followed a chronic course, becoming aggravated during cold weather and improving during warm weather. They made the interesting observation that there was spontaneous recovery in girls after marriage and in boys after they became 20 to 22 years old. This has not been true in our patients.

Fischl,[28] in 1931, suggested that more care be used in applying names to certain papuloneerotic lesions, in order to forestall confusion. Particular care should be taken in those conditions of uncertain etiology which have a resemblance to tuberculosis, but in which a relationship never has been proved. It would appear, from this paper, that among other conditions he probably had perniosis in mind.

Mayer and Cajkovac,[29, 30] in 1932, described the seasonal variation in nonspecific sensitivity of the skin in eczema and related diseases. The peak was said to appear both in the spring and in the fall in the eczematous patients, as well as in the patients with lichen vivae and prurigo hebrae. Whether they had cases of pernio mixed with these groups it is difficult to say, since, as mentioned above, pernio of the hands was first described by Corlett,[8] in 1891, and called "eczema." Most dermatologists of that period considered it an eczema.

Sannicandro,[31] in 1932, described a case of a 60-year-old man with a skin lesion which took on the character of efflorescences that presented some of the histologic features of pernio; but here the distribution was more extensive than in many of the cases we have seen, and no seasonal variation was mentioned.

Buerger,[32] in 1937, subdivided this condition (pernio) into four stages: (1) perniosis folliculosis; (2) infiltrating pernio; (3) bulbous stage; and (4) ulcerated form.

Knight,[33] in 1938, outlined a form of treatment for erythrocyanosis frigida. However, he merely made the statement that Bazin's disease, erythema induratum, affected girls, and elucidated no further.

During the past six years we have had the opportunity of studying ten patients with this disfiguring condition. It is fairly common in the North Temperate Zone, and occurs predominantly among women. Careful analysis shows that all patients suffering from this syndrome have a similar history. They present essentially the same clinical features and pathologic changes. Detailed reports of four typical cases will serve to illustrate our observations.

CASE REPORTS

CASE 1.—L. H., a woman, aged 29 years, was first admitted April 10, 1933. She was born May 18, 1903, in the United States. The family history was negative except that a brother had died of malignant hypertension. She had had hypertension for eleven years. Her first pregnancy had resulted in a miscarriage at five and one-half months because of toxemia and hypertension. The second and third children were stillborn at full term, in 1928 and 1929. In 1930, a fourth pregnancy was terminated in the sixth month by cesarean section because of a kidney complication. She had suffered from sore throats almost continuously until ten years before ad-

mission. The patient had never had edema, nocturia, or hematuria, but had had frequent throbbing headaches, with vertigo, nausea, and vomiting. She stated that she had complained of "growing pains" and rheumatic pains every winter since the age of 10 years.

Since the age of 7 years she had developed ulcers on her legs annually. These had occurred with the onset of cold weather in the fall, and had persisted until warm weather returned. Numerous small ulcers appeared simultaneously. Many of the ulcers had begun around the internal malleoli and gradually extended up to the calves. When they healed, they left a violaceous discoloration which would never disappear completely. It was in these areas that succeeding ulcers would form during the next cool spell. This condition was diagnosed as tuberculosis of the skin. She was given "gold injections," apparently with slight temporary improvement. Her feet became extremely white and painful when slightly chilled, but her hands never showed the same sensitivity to cold. During the months when the ulcers were open she had a low-grade fever at night, associated with drenching sweats, resulting in an annual winter weight loss of 30 to 40 pounds (one-fourth to one-third her normal body weight).

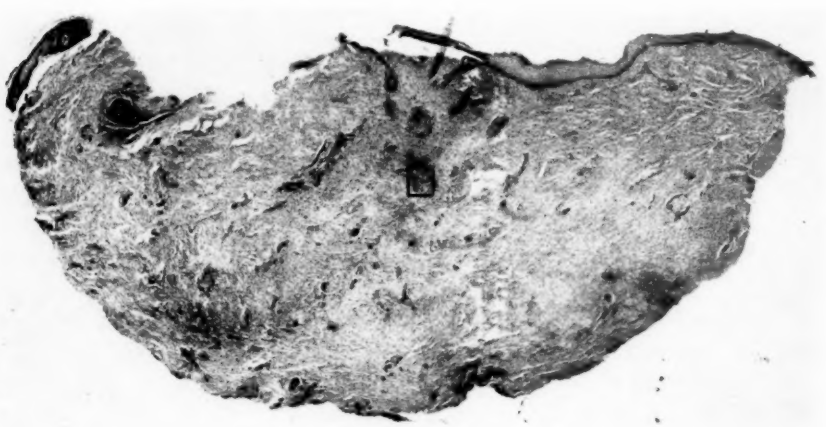

Fig. 1.—Case 1. Photomicrograph (×40) of lesion. Note prominent blood vessels in corium and necrosis in corium.

The physical examination on April 10, 1933, revealed that the tonsils were buried and that there was a profuse posterior nasal discharge. The teeth were carious; the gums were infected and bled easily. There were a few slightly enlarged cervical glands which were not tender, and a similar group of glands was present in the right axillary region. The lungs were essentially normal. The heart was found to be enlarged to the left. There was a systolic thrill and a prolonged systolic murmur over the mitral area. The pulmonic second sound was accentuated, and was louder than the aortic second. The blood pressure was 220/120. There were twenty to thirty reddened, indurated, tender, broken-down, nondischarging ulcers scattered bilaterally over the legs. Many superficial atrophic scars of small healed lesions were distributed through the same areas. The left radial artery was not palpable; the dorsales pedium were not palpable, and there was marked dependent cyanosis. No oscillometric readings could be made because of the presence of the ulcers.

Laboratory examination revealed no evidence of tuberculosis in the lungs, although, roentgenographically, there was evidence of an old, puerile, tuberculous focus at the hilus, and the Mantoux reaction was positive at a 1:1,000 dilution. She had an

aortic type heart. The electrocardiogram was normal. The basal metabolic rate was plus 4. The blood Wassermann reaction was negative. The erythrocyte count was 4,600,000, and the leucocyte count, 7,650. The hemoglobin was 11.46 Gm. (79 per cent), and the color index, 0.86. The differential leucocyte count showed polymorphonuclers, 76 per cent; eosinophiles, 1 per cent; monocytes, 3 per cent, small lymphocytes, 6 per cent; and large lymphocytes, 14 per cent. Repeated urine examinations were negative except for a trace of albumin and an occasional hyaline cast. Chemical examination of the blood revealed nonprotein nitrogen, 37.2 to 39.8 mg.; urea nitrogen, 14.6 to 15.5 mg.; cholesterol, 470 mg.; and sugar, 107 mg., per 100 ml. blood.

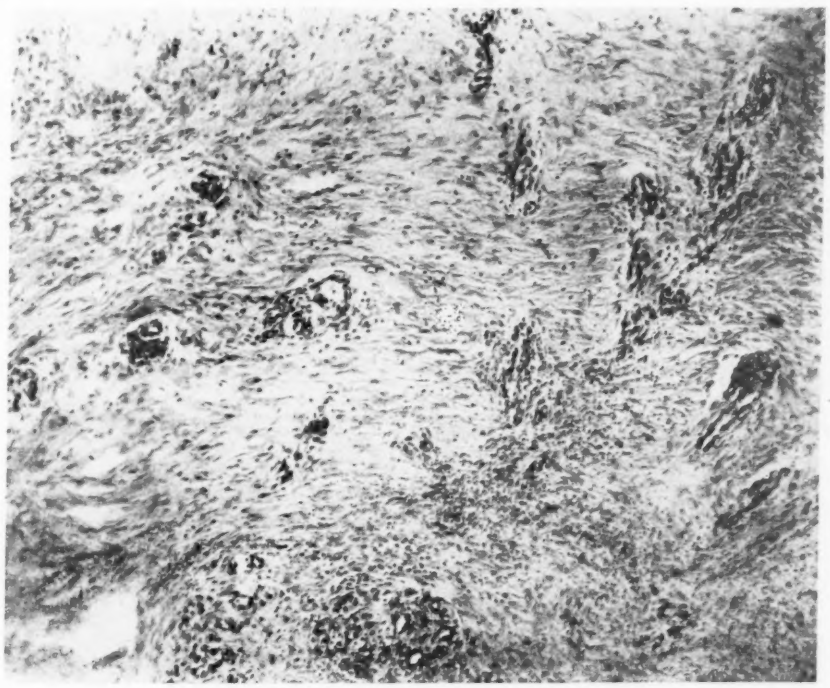

Fig. 2.—Case 1. Photomicrograph (×180), enlargement of box in Fig. 1. Note small vessels surrounded by cuffs of polymorphonuclear and small mononuclear cells. Endothelial proliferation. Multinucleated cells are present but difficult to make out in this plate.

Biopsy of a lesion showed no evidence of tuberculosis. There was the usual cornification of squamous epithelium, without any evidence of hyperkeratosis or acanthosis. The corium contained many prominent blood vessels which were surrounded by small cuffs of polymorphonuclear and small mononuclear cells, as well as young, spindle-shaped fibroblasts. The vessels were also unusual in that they almost invariably showed endothelial proliferation, with occasional cells in mitotic division. Clusters of newly proliferated vessels suggested newly formed granulation tissue. There was some necrosis in the corium, with considerable recent hemorrhage, and there was also some evidence of fibroblastic proliferation, as well as a rare multinucleated cell. The process was a chronic, necrotizing one, in which healing by organization was prominent. The vascular reaction was the most conspicuous feature.

Case 2.—A. H., a woman, 19 years of age, was first admitted April 5, 1938. She was born in the United States. The family history and past history were irrelevant.

Fig. 3.—Case 2. Leg lesions. Posterior aspect. Note ulcer and pigmentation.

Fig. 4.—Case 2. Leg lesions. Lateral aspect. Note small ulcer above malleolus of right leg, and small ulcer on left leg, also pigmentation.

Following an injury to her right leg in March, 1937, the patient had noticed red blotches which were elevated above the surrounding surface. They had first appeared on the posterior surface of the lower third of the right leg. The lesions became more raised and scaly, and then appeared to come to a head, to ulcerate, and to heal. After two weeks in bed she still had the red blotches. The same type of lesion soon appeared on the left leg. During the summer of 1937 the lesions healed. However, in November, 1937, although there was no new injury to the leg, several lesions of the same type again appeared, each one developing into an ulcer. No treatment was instituted. In the late spring (May, 1938), all the lesions disappeared. There was a slight injury to the right leg about Christmas, 1938, when the condition returned and both legs ulcerated as previously. When seen late in the summer of 1939, the lesions had not completely healed, but were definitely improved and were confined to the lower third of both legs, along the medial and posterior surfaces. As in the other cases, when the lesions began to appear they were excruciatingly painful, but, after they ulcerated, the pain was less acute.

Fig. 5.—Case 2. Medical aspect of right leg, showing marked pigmentation and healing ulcers.

Physical examination on April 5, 1938, showed nothing abnormal except the leg lesions. Her blood pressure was 100/50, and the oscillometric readings were normal, as were the capillary studies. Roentgenologic examination of the lungs revealed nothing abnormal. The basal metabolic rate was plus 4; the Mantoux reaction was positive at 1:1,000; and the blood Wassermann reaction was negative. The erythrocyte count was 4,380,000, the leucocyte count, 8,000, the hemoglobin, 11.6 Gm. (70 per cent), the color index, 0.86, and the platelet count, 270,000. The

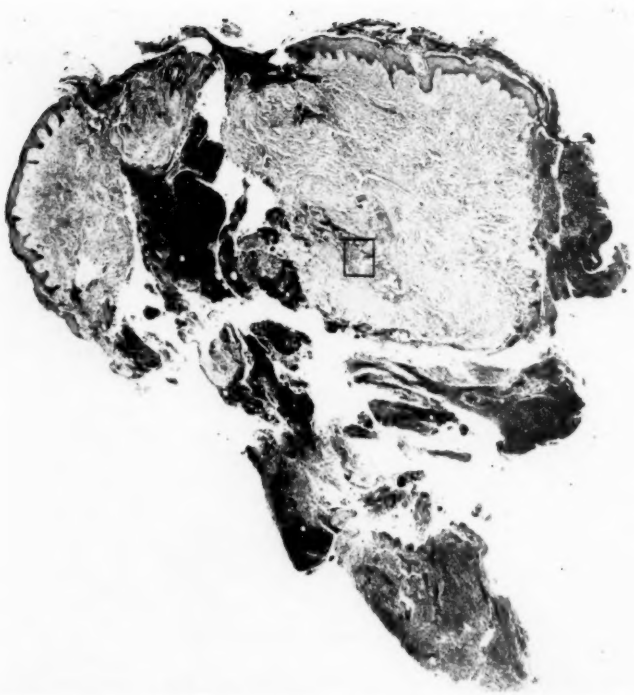

Fig. 6.—Case 2. Photomicrograph (×28) of lesion. Note small zone of ulceration.

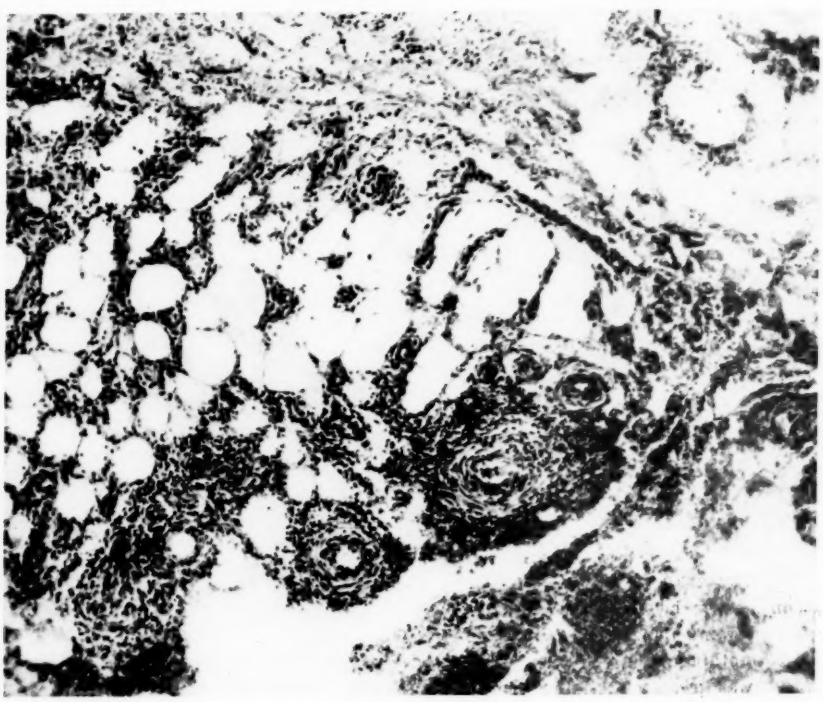

Fig. 7.—Case 2. Photomicrograph (×180), enlargement of box in Fig. 6. Panniculus is extensively necrotic, capillaries unusually prominent. Leucocytes as well as small lymphocytes infiltrate the adipose tissue. Note endothelial thickening and perivascular ring of fibrous tissue.

differential leucocyte count showed polymorphonuclears, 70 per cent; eosinophiles, 1 per cent; monocytes, 1 per cent; small lymphocytes, 26 per cent; and large lymphocytes, 2 per cent. A routine urine examination was negative, and the results of the Mosenthal two-hour renal function test were normal. Chemical examination of the blood revealed nonprotein nitrogen, 24 mg.; urea nitrogen, 10 mg.; and calcium, 9.3 mg., per 100 ml. serum. Ascorbic acid studies indicated the following: fasting blood content, 0.54 mg. per 100 ml. of plasma; saturation test,[19] 355 mg. excreted in the twenty-four hours following injection of 1,000 mg.

Biopsy of a lesion revealed no evidence of tuberculosis. Except for a small zone of ulceration, the overlying squamous epithelium was not abnormal. Immediately beneath the basal cell layer there was an extensive leucocytic cellular reaction which was diffusely infiltrating the subcutis. The capillaries of this region were unusually prominent as a result of endothelial and pericapillary fibroblastic proliferation. The panniculus was extensively necrotic, containing many nuclear fragments, but showing no true caseation. Polymorphonuclears, as well as small lymphocytes, infiltrated the adipose tissue, and there was considerable fibrosis. The most conspicuous feature in the panniculus was the vascular change, which consisted of a chronic angiitis. Not only was the endothelium greatly thickened, but there was also a striking perivascular ring of fibrous tissue containing many cells, chiefly of the lymphocytic series.

Fig. 8.—Case 3. Anterior aspect. Ulcer over right internal malleolus and over dorsum of foot. Extensive pigmentation of both legs.

CASE 3.—O. H., a woman, aged 39 years, was first admitted Sept. 19, 1938. The family history was negative. The past history was not significant, except that in October, 1937, she had developed an eczematous condition involving the flexor surfaces of the legs, back, and hands, in that sequence. Roentgen therapy had been given. The condition had cleared up in ten weeks; its etiology was unknown.

At the age of 14 years the patient had developed red, indurated areas, which caused pain on pressure, on the inner and posterior surfaces of both legs. These had become inflamed and then had healed without ulceration, followed by complete disappearance of the lesions. The patient had had a similar attack in the fall of her eighteenth year, but for the first time the indurated, raised areas had become ulcerated. For the next seven years the legs were perfectly normal. At the age of 25 years the lesions had recurred after she had gone swimming late in the summer. The condition of her legs was such that she had remained in bed most of the time from October until June, wearing a gelatine boot which was changed at frequent intervals. The legs healed, and she remained well for three years. From her twenty-eighth year to the time of examination, a period of eleven years, her right leg had never completely healed, although it was definitely improved during the warm months of the year. The left leg had been free of ulceration for four years.

Fig. 9.—Case 3. Lateral aspect. Extensive pigmentation of left leg. Right leg has ulcers over dorsum and below external malleolus, and marked sclerodermic changes.

In October, 1938, she had excruciating pain across the right instep, and ulcers appeared between three toes of the right foot. Ulcers then appeared over the dorsum of the foot, and a single, large lesion persisted in this area. The pain in the reddened areas was knifelike in character. The areas were discrete and changed from red to violaceous in color. When the patient opened these lesions with a needle, a dark red serum exuded for a day, then a yellowish serum oozed out, and the lesions thereafter began to ulcerate, with cessation of pain. The ulcers took from four to five weeks to heal. The healed areas were deeply pigmented. On these pigmented areas the next year's crop of lesions became engrafted. The lesions were

open almost all winter (1938-1939), and the patient was confined to the house from October until the end of February.

Physical examination revealed nothing abnormal except the lesions on the legs. The skin was deeply pigmented and sclerodermic from the knees downward. A large, ulcerated lesion was present over the internal malleolus, and another over the dorsum of the right foot. The left leg merely showed the pigmentation, scleroderma, and evidence of healed ulcers. The oscillometric readings were normal.

Fig. 10.—Case 3. Medial aspect, right leg and foot. Ulcer over internal malleolus. Marked pigmentation.

A roentgenogram of the lungs showed an old, inactive tuberculous focus in the right hilus, as well as an old Ghon node.

The sputum contained no tubercle bacilli; the basal metabolic rate was minus 15 per cent; the Mantoux reaction was positive at 1:1,000. The blood Wassermann reaction was negative. The erythrocyte count was 3,970,000; the leucocyte count, 5,000; the hemoglobin, 78 per cent; and the color index, 0.98. The differential leucocyte count showed polymorphonuclears, 68 per cent; eosinophiles, 2 per cent; small lymphocytes, 21 per cent; and large lymphocytes, 8 per cent. The urine examination was negative. Chemical examination of the blood showed that the urea nitrogen was 10 mg.; the uric acid, 3.7 mg.; the chlorides, 485 mg.; and the true glucose, 85 mg., per 100 ml. of blood. The sedimentation rate, by the Westergren method, was 18 mm. in 60 minutes.

Biopsy of a lesion showed no evidence of tuberculosis. There were an extreme degree of hyperkeratosis and a fairly large abscess within the squamous epithelial layer. It was apparent that this represented a chronic process of long standing, in which ulceration undoubtedly played a conspicuous role. This was indicated by the fact that nests of epithelium lay in isolated foci in the subcutaneous connective tissue. In this case, the angiitic reaction in the subcutis was a conspicuous feature.

Fig. 11.—Case 3. Photomicrograph (×50) of lesion. Note hyperkeratosis and abscess.

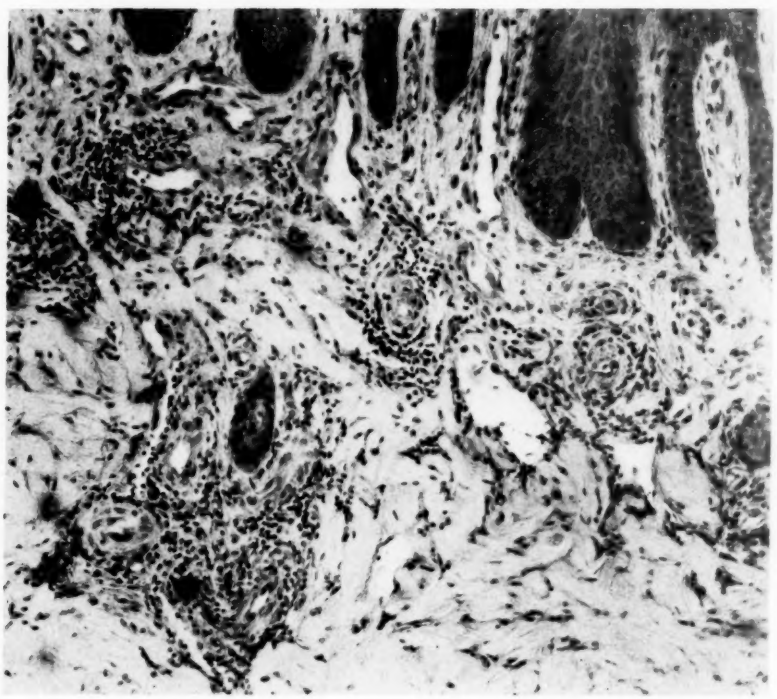

Fig. 12.—Case 3. Photomicrograph (×240), enlargement of box in Fig. 11. Nest of epithelium in the subcutaneous connective tissue. Vessel walls are greatly thickened with almost obliteration of lumina. Mitotic figures present but difficult to see in plate.

The vessel walls were greatly thickened, which had in some cases led to almost complete occlusion of the lumina. Each of the vessels thus involved was also surrounded by collections of neutrophilic leucocytes, lymphocytes, and large mononuclear cells. There was an extreme degree of necrosis in the panniculus adiposis. Some of the necrosis even suggested caseation. The chronicity of the condition was indicated by the extensive granulation tissue on the margins of the necrosis. An

interesting feature of the microscopic appearance was the presence of many cells in division, both in affected vessels and in the dermis.

CASE 4.—R. P., a woman, aged 39, was first admitted Feb. 7, 1939. She was born in Italy. Her family and past history were irrelevant. She had had two miscarriages and one full-term delivery, the latter in 1929.

Fig. 13.—Case 4. Ulcers over external and internal malleoli, dorsum of right foot, and between toes.

Fig. 14.—Case 4. Lesion in region of tendon Achilles.

In September, five years before, the patient first began to complain of cold, itchy feet. This was followed very shortly by blistering, with ulceration of the inner surface of the left ankle. Each summer the lesions would heal, but they appeared again each fall. The ulcers were treated with salves during this period in a skin clinic.

Whenever the patient was exposed to cold, she would have a burning feeling, followed by itching which was a sign of the initiation of the leg lesions. The areas would become bluish-red, and some even looked like subcutaneous hemorrhages. The lesions would vary in size from a petechial spot to a dime. Severe, knifelike pain which was worse at night was felt in the discolored areas. After two days to three weeks of this discomfort, a blister would form, exuding a pinkish or yellowish odorless exudate, followed by ulceration. A scab would form and the lesion heal. If at this stage the legs were injured by exposure or in any other way, the lesions would ulcerate again. Each crop of lesions usually began simultaneously and healed simultaneously. The lesions were confined exclusively to the legs, and almost always to the lower third. There had been a few lesions over the dorsum of the foot and toes. The legs had never been completely healed during the winters of the past five years. However, they were completely healed in the summer of 1938, and remained so until late October. Although the healing was complete, a violaceous area would remain, and there the next year's crop of lesions would appear. These pigmented areas never disappeared. The severe pain would usually last until ulceration occurred and then progressively diminish.

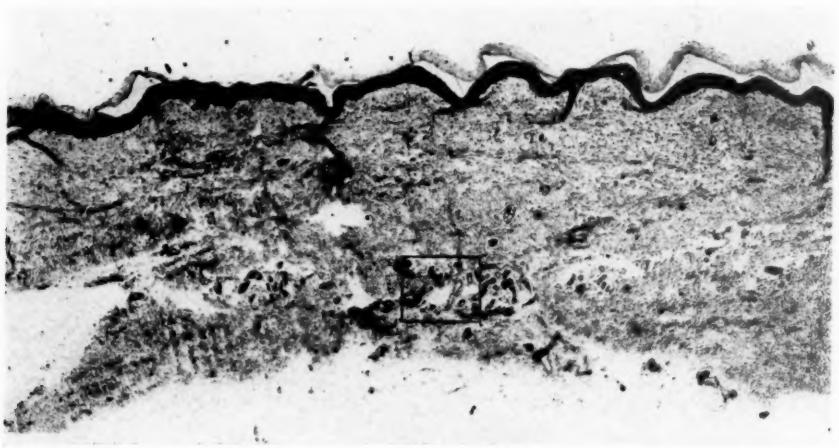

Fig. 15.—Case 4. Photomicrograph (×65) of typical lesion. Note angiitis in subcutis, and fibrosis.

Physical examination showed nothing abnormal except the leg lesions. There were large, square-shaped, granulating lesions on the inner aspect of the ankles, extending backward to the calves. There was marked ulceration of the ankles, dorsums of the feet, and toes. The dorsalis pedis and posterior tibial vessels were normal. There were no color changes when the feet were either elevated or dependent. There were slight varicose veins on both legs. The oscillometric readings were normal.

A roentgenogram of the lungs revealed nothing abnormal. The basal metabolic rate was plus 2 per cent, and the blood Wassermann reaction was negative. The erythrocyte count was 4,660,000; the leucocyte count, 9,550; the platelet count, 200,000; the hemoglobin, 77 per cent; and the color index, 0.78. The differential leucocyte count showed polymorphonuclears, 71 per cent; small lymphocytes, 28 per cent; and large lymphocytes, 1 per cent. Chemical examination of the blood revealed that the urea nitrogen was 10 mg.; the nonprotein nitrogen, 26 mg.; the inorganic phosphate, as P, 3.3 mg.; and the calcium, 10.7 mg., per 100 ml. of serum. Ascorbic acid studies showed a fasting blood content of 1.09 mg. per 100 ml. of plasma; in the saturation test, 430 mg. were excreted in the first five hours,

and a total of 475 mg. in the twenty-four hours following injection of 1,000 mg. (The normal amount of ascorbic acid excretion in the urine following a 1,000 mg. test dose is 480 or more mg. in five hours, and 500 or more mg. in twenty-four hours.[34]) The sedimentation rate, by the Westergren method, was 15 mm. in sixty minutes. Fractional gastric analysis revealed a normal acidity curve. All the cold sensitivity tests (exposure to chilling and application of ice directly to the skin) were negative.

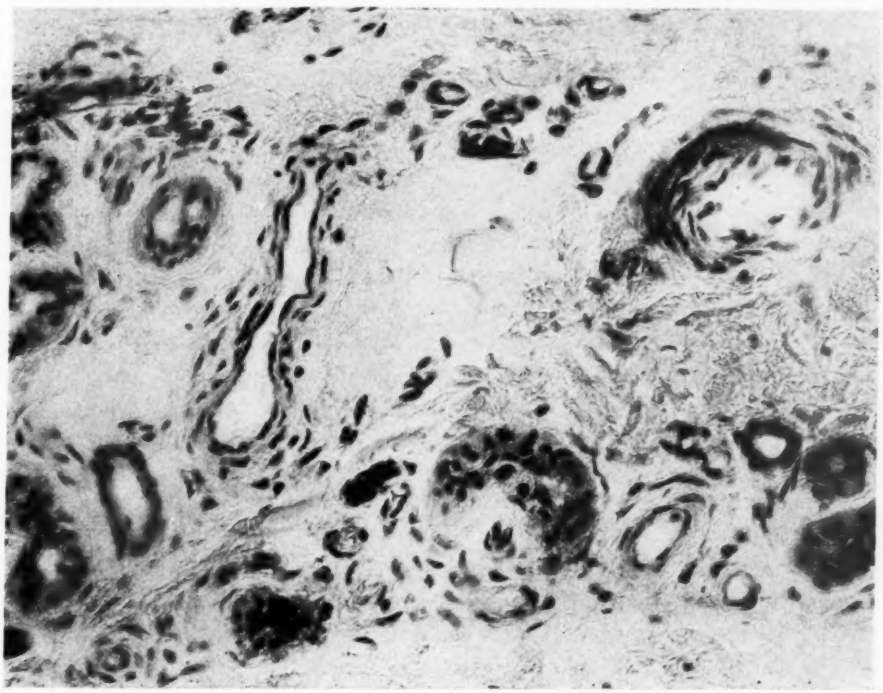

Fig. 16.—Case 4. Photomicrograph (×650), enlargement of box in Fig. 15. Isolated nests of epithelium. Endothelial proliferation and perivascular infiltration.

Biopsy of a lesion revealed no evidence of tuberculosis. There were superficial cornification and exfoliation of the stratified squamous epithelium. There was an increase of the fibrous tissue in the underlying corium, with marked edema and a smoothing of the rete pegs. The sweat glands were displaced and their coils were separated by the increased, edematous, connective tissue fibers. A mild degree of mononuclear cell infiltration was noted. The deeper layers of the epidermis were pigmented, and the lymph spaces between the cells were dilated, with a tendency to vesicle formation. The capillaries showed evidence of proliferation. In the subcutis the vessel walls were greatly thickened, which had caused occlusion of the lumina, and there was marked perivascular infiltration. The striking feature was an angiitis.

DISCUSSION

These cases are strikingly similar in several respects. The leg lesions appeared in adolescence or early adulthood, and the attacks were precipitated by exposure to cold, usually coming in the late autumn. The condition continued throughout the winter, at which time the lesions were at the height of their activity.

The lesions lasted a varying length of time, but gradually subsided, until, in the late spring or early summer, they healed, leaving scar formation and pigmentation. In some cases the ulcers may have failed to heal completely during a summer. The next fall there was an exacerbation of symptoms and a recrudescence of lesions.

There were burning and itching, then redness, followed by the appearance of discrete, red, raised areas, with induration in which excruciating pain was felt. This was followed by a more pronounced elevation of the lesions, which became a deeper red or violaceous color while the skin became very thin. Next there was an exudate of pink or black-tinged serum, giving way to a yellowish exudate, true ulceration, and slow healing, with cessation of pain. Lastly, there were scar formation and deep pigmentation of the scarred area. Not infrequently these lesions failed to progress to actual ulceration.

In each case, the most prominent histologic feature of the biopsy specimen was an angiitis, with necrosis of the panniculus adiposis and a definite inflammatory reaction, but there was absolutely no evidence of a tuberculous condition.

Pernio has long been considered a dermatologic problem, when, in reality, it is a vascular problem, with secondary dermatologic manifestations. It has been rather inadequately described in the American literature, and seems to be of sufficient importance and interest to warrant a refocusing of attention on it.

The lesions have a disfiguring effect on the limbs, leaving them permanently scarred when the process is not in the stage of ulceration. This constitutes a mental handicap to its victims, in this day of thin stockings and short skirts. It is a debilitating condition, necessitating long periods in bed, or indoor rest, especially during the colder months of each year.

It is interesting that Corlett's patients had their lesions on the hands and wrists, while ours and most of the German patients recently reported had theirs on the legs. In 1896, during the cold weather, women wore long drawers, heavy stockings, high boots, long skirts, and coats; the only parts of the body exposed to the cold were the hands. Today, women do not usually wear long drawers, heavy stockings, or high-top shoes; skirts are never lower than calf length for everyday wear, and stockings are silk. The shoes are perforated and thin, with light soles. Consequently, from the mid-thigh down there is today little or no protection in a woman's clothing against the cold. This exposes a large area of the body surface to cooling, with a resultant great loss of heat by radiation. In order to help maintain a constant body temperature and prevent heat loss, the vessels in the legs are necessarily forced into vasoconstriction, resulting in anoxemia of the supplied tissues. This, in all probability, affects primarily the arterioles, and, secondarily, the tissues supplied by the minute vessels of the skin and the subcutaneous

zones, which bear the brunt of the anoxemia. The greater clothing protection which men customarily have probably accounts for the present rarity of pernio in the male sex.

SUMMARY

Evidence has been presented that pernio is a vascular disease, affecting the smaller vessels of the skin, causing anoxemia of the supplied tissue, and resulting in necrosis and ulceration. Later, a definite sclerodermic-like change in the skin may occur. It is precipitated by a downward change in temperature, not necessarily freezing, but by mere cooling. This may occur at a temperature which, under ordinary circumstances, would not cause an appreciable change in normal skin, but which causes definite changes in susceptible persons. Characteristically, exacerbations of this condition occur in the fall and winter, and regression in the summer. In long-standing cases, however, complete recovery may not occur in the summer. We believe that this is due to the extensive vascular changes in the tissues.

We have been able to demonstrate giant cells in our sections, but we have found no evidence of tuberculosis. We have very carefully checked our patients clinically with this in mind, so that we can make the definite statement that our patients were free from clinical and roentgenologic evidence of active tuberculosis at the time their leg lesions were active.

The following tentative criteria are suggested for the diagnosis of pernio.

1. It may occur in both sexes, predominantly in females.

2. It usually commences in adolescence or early adulthood.

3. It is associated with cool or cold weather and may show spontaneous recovery in warm weather.

4. The lesions have a predilection for exposed areas, particularly the lower third of the leg, around the internal malleolus and calf. They may extend down to the dorsum of the foot and toes, and up the legs to below the knees.

5. The clinical course of these lesions may be characterized briefly as (a) the formation of a reddened area which later becomes elevated, hard, and very painful; (b) this becomes violaceous and fluctuating; (c) it opens, producing an ulcer; (d) this oozes, drains, and heals, becoming less painful; (e) a violaceous scar remains; and (f) the following winter ulceration tends to recur in the same area.

6. There is a definite pathologic picture. Most characteristic is, first, an angiitis of the smaller vessels; secondly, necrosis of the fat; and, thirdly, the presence of giant cells. This pathologic picture, while characteristic of all our cases, must not be considered morphologically specific, for a number of other vascular conditions present similar histologic changes. They all represent a chronic irritative process in

the subepidermal tissue. Whether the irritative phenomenon is secondary or primary cannot be definitely stated.

Treatment of this condition is not specific, but the best results in our hands have been achieved by triweekly treatments with acetyl-beta-methylcholine chloride (mecholyl) by iontophoresis, and by protection of the legs with proper clothing from undue exposure. Living in a warm climate should minimize the occurrence of the lesions.

Early recognition of this syndrome, and treatment as suggested, will help to prevent permanent disfigurement and long periods of incapacitation.

The authors are grateful to Dr. Harry M. Zimmerman, of Yale University Medical School, for his kindness in reviewing their pathologic material.

REFERENCES

1. Hallam, R.: Enigma of Chilblain, Brit. M. J. **1**: 215, 1931.
2. (a) Hawthorn, M. M., and Vigne, P.: Un cas d'érythème induré de Bazin chez un jeune homme de 24 ans, Marseille-méd. **1**: 696, 1934.
   (b) Vigne, P., and Dusan, J.: Un autre cas d'érythème induré de Bazin type Hutchinson, Marseille-méd. **1**: 699, 1934.
3. Bazin, A. P. E.: Lecons theorique et cliniques sur le scrofule, ed 2, Paris, 1861, A. Delahaye.
4. Pautrier, L. M., and Yelmo, A.: Bazin's Erythema of Both Legs in Patients Who Previously Had Symmetrical Supramalleolar Erythrocyanoses, Bull. Soc. franç. de dermat. et syph. **42**: 859, 1935.
5. Telford, E. D.: Erythrocyanosis, Brit. Encyc. Med. Practice **5**: 182, 1937.
6. David, Jean: Erythrocyanose sur malleolaire étude pathogenique, clinique et Therapeutique, 24 cm., No. 63, Paris, 1929, Jouve & Cie.
7. Schulde, Reinhold: Ueber Erythrocyanosis Cutis Symmetrica mit besonderer Berücksichtigung zweier Falle, Frankfurt Theses, Frankfurt a. M., Werner u. Winter, 1927.
8. Corlett, W. T.: Cold as an Etiological Factor in Diseases of the Skin, Tr. Am. Dermat. A. **18**: 95, 1894.
9. Gallois, P.: Engelure des jambres, J. méd. de Paris **48**: 532, 1929.
10. Grschebin, S.: Concerning the Identity of Erythema Induratum of Bazin and Lupus Pernio, Urol. & Cutan. Rev. **39**: 477, 1935.
11. Bartman, Joseph: Contribution à l'étude du lupus pernio, Paris Theses, Paris, 1925, Ed. Medicales.
12. Bescone, Jeanne: Contribution à l'étude du lymphogranulome Benin (lupus pernio vrai), Paris Theses, Paris M. Lac, 1928.
13. Nardelli, L.: Bazin's erythema induratum and acrocyanosis, Gior. ital. di dermat. e sif. **67**: 83, 1926.
14. Klingmuller, F., and Dittrich, O.: Ueber Frostschaeden, Dermat. Ztschr. **49**: 1, 1926.
15. Perutz, A.: Ueber eine eigenartige Lokalisation von Frostschaeden, Dermat. Wchnschr. **88**: 709, 1929.
16. Kreindler, A., and Elias, H.: Zur Klinik und Pathogenese der juvenilen Acrocyanose, Ztschr. f. Kinderh. **50**: 608, 1931.
17. Ravitch, M. L.: Focal Infection in Relation to Certain Dermatoses, J. A. M. A. **67**: 430, 1916.
18. Haldin, Davis: Skin Diseases in the Winter, Practitioner **141**: 741, 1938.
19. Woringer, F.: Histological Picture of Bazin, Bull. Soc. franç. de dermat. et Syph. **45**: 1316, 1938.
20. Corlett, W. T.: Cold as an Etiological Factor in Diseases of the Skin, 1894, Eleventh International Medical Congress in Rome, p. 153.
21. Corlett, W. T.: Dermatitis Hiemalis With a Consideration of Its Pathological Anatomy, 1896, Third International Congress of Dermatology in London, p. 622.
22. Niles, H. D.: Winter Eczema of the Arms, Arch. Dermat. & Syph. **39**: 474, 1939.

23. (a) Telford, E. D., and Stopford, J. S. B.: Some Experiences of Sympathectomy in Anterior Poliomyelitis, Brit. J. Surg. **18**: 557, 1931.
(b) Telford, E. D., and Stopford, J. S. B.: Some Experiences of Sympathectomy in Anterior Poliomyelitis, Brit. M. J. **2**: 770, 1933.
(c) Telford, E. D.: Lesions of the Skin and Subcutaneous Tissue in Diseases of the Peripheral Circulation, Arch. Dermat. & Syph. **36**: 952, 1937.
24. Eugman, M. F.: The Skin: A Mirror to the System, J. A. M. A. **73**: 1565, 1919.
25. Von Norden, W.: Die neuere frostbeulen Behandlung, München. med. Wchnschr. **75**: 691, 1928.
26. Dittrich, O.: Ueber Frostschaeden, Arch. f. Dermat. u. Syph. **157**: 1, 1929.
27. Lewis, Thomas: Observations Upon the Reactions of the Vessels of the Human Skin to Cold, Heart **15**: 177, 1929.
28. Fischl, F.: Identity of Dermatitis Nodularis Necrotica and Papulonecrotic Tuberculid, Dermat. Wchnschr. **92**: 50, 1931.
29. Mayer, R. L., and Cajkovac, S.: Seasonal Variation in Nonspecific Sensibility of the Skin in Eczema and Related Diseases, Arch. f. Dermat. u. Syph. **126**: 325, 1932.
30. Cajkovac, S., and Mayer, R. L.: Seasonal Differences in Skin Sensibility and in Frequency of Eczematous Diseases, Lijecn vjes **54**: 268, 1932.
31. Sannicandro, G.: Hitherto Undescribed Skin Diseases, Pigmented Papuloverrucous Dermatosis With Connective Tissue Hyalinosis, Arch. f. Dermat. u. Syph. **166**: 58, 1932.
32. Buerger, Leo: Chilblain, Nelson Loose-Leaf Medicine **2**: 664C-K, 778A-I, 1937.
33. Knight, G. C.: Sympathectomy in the Treatment of Erythrocyanosis Frigida and Chronic Oedema of the Leg, St. Barth. Hosp. Rep. **71**: 173, 1938.
34. Wright, I. S., Lilienfeld, A., and MacLenathen, E.: Determination of Vitamin C Saturation: A Five Hour Test After an Intravenous Test Dose, Arch. Int. Med. **60**: 264, 1937.

DISCUSSION

DR. IRVING S. WRIGHT, New York.—The last two papers emphasize the fact that livedo reticularis and pernio in particular, and I believe this holds for numerous other conditions, have been in the past erroneously considered as diseases of the skin, and treated primarily by the dermatologist, frequently by means of the application of salves, ointments, and perhaps superficial roentgen therapy.

Now, this is not to be regarded primarily an endeavor on the part of the workers in the field of vascular disease to try to move these diseases from one specialty to another, but it is important that we change our conception of them. In other words, as long as we treat these diseases as if they were only superficial local lesions, and do not understand the fundamental vascular changes underlying them, I can see no hope for solution either from the viewpoint of the pathology, etiology, or treatment.

That, in itself, constitutes in my mind a very important contribution to thought in this field, and I do not doubt that other so-called skin diseases will yield to similar types of study. Certainly that has been true of lupus erythematosus disseminatus, which has been studied so capably by Libman and Sachs and others.

DR. NORMAN E. FREEMAN, Philadelphia.—Since Dr. McGovern and Dr. Wright feel that this condition is associated with normal vasoconstricting activity, I wonder if they have had any experience with sympathectomy in the treatment.

We recently saw a patient who had a combination of livedo reticularis and pernio, on whom we did a paravertebral novocaine block, anesthetizing the sympathetic lumbar ganglia. With the blanching of the reticular areas of the livedo reticularis, there was also a change from the cyanotic appearance of these lesions of pernio to a nice, pink color.

DR. NELSON W. BARKER, Rochester, Minn.—Although the clinical pictures of pernio and livedo reticularis are different, I am much impressed with the similarity of the pathologic changes in the arterioles of the skin. There is reason for believing that

this type of vascular lesion is not a specific one, for it is also seen in a number of other conditions in which the clinical pictures are different from one another. In livedo reticularis, the temperature of the skin is subnormal for long periods of time, both when the patient is exposed to cold and when he is in a normal environmental temperature. It is possible that this lowered temperature of the skin may be a factor in the production of the pathologic changes in the arterioles.

DR. HAROLD D. LEVINE, Concord, N. H.—I should like to ask Dr. McGovern whether these patients were tested for sensitivity to cold ("cold allergy"), and whether she has any information as to the nature of the condition in its very inception. It would be of interest to know if in the early attacks the lesions are urticarial.

DR. TERESA MCGOVERN, New York.—Sympathectomy was not performed in any of our cases of pernio; consequently, we are not in a position to pass comment on this type of therapy. The lesions in pernio are not of an urticarial character, but are merely erythematous. This lesion has none of the characteristics of true cold allergy, as first described by Horton and Brown. The cold tests were done on all of these patients and none was sensitive to cold, as we understand cold sensitivity.

INCIDENCE OF TYPES OF HEART DISEASE AMONG 30,265 AUTOPSIES, WITH SPECIAL REFERENCE TO AGE AND SEX

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Minneapolis, Minn.

THE relative frequency of the various types of heart disease evidently is not the same in all localities. Rheumatic types are more common in the northeastern states than in Minnesota, and syphilitic types are more common in some of the southern states.

It is difficult to obtain reliable information concerning the incidence of heart disease from death certificates because of the uncertainties of diagnosis. It is also difficult to find a large, nonselected, autopsy series.

White,[1] in analyzing the literature on the incidence of the types of heart disease, stated: "Accurate information about the community incidence of heart disease is as yet scarcely available anywhere in the world."

The purpose of the analysis in this paper is to give the incidence of the types of cardiac disease encountered among the autopsies which have been performed at the University of Minnesota Medical School during 1910 to 1938, inclusive. During this period there were 19,685 autopsies on males and 10,580 on females, or a total of 30,265, not including those on stillborn infants. In this same period there were 4,678 deaths from noncongenital cardiac disease (15.45 per cent of the autopsies). Congenital heart disease is not included because it occurred mainly in stillborn babies; the small number of cases in persons older than babies would increase the general incidence by less than 0.5 per cent.

The only cases included were those in which death was caused by cardiac failure, or by conditions fairly definitely associated with cardiac failure, such as uremia, or cerebral hemorrhage with hypertension, or rupture of a syphilitic aneurysm of the arch of the aorta. In most of these, when death was not due entirely to conditions in the heart itself, there was an overlapping of heart disease, so that death would evidently have resulted soon from cardiac failure. Cases of valvular deformities or cardiac hypertrophy in which death was caused by something other than heart disease, such as an automobile accident, were not included. The actual incidence of cardiac disease in this series was, therefore, even greater than that reported in this paper.

From the Department of Pathology, University of Minnesota.
Received for publication Feb. 3, 1941.

The percentage of cardiac deaths in this autopsy series, we believe, is near to the percentage of cardiac deaths in the general population in the State of Minnesota. The autopsy material was fairly representative and nonselected. The autopsies were done in general and private hospitals, on private patients of practicing physicians, and on the coroner's service, which was fairly large. In 1938 the percentage of autopsies was high, namely, 25 per cent in Minneapolis and 10 per cent in the State of Minnesota. The percentages in the preceding years, while somewhat less, were also high. This material, because of its volume, wide distribution, and large autopsy percentage, appears to be as good as any that could be found for making an approach to a statistical study of the incidence of the different types of cardiac disease.

All cardiac autopsy records were restudied. Many of the cases were observed personally.

The 4,678 cases were analyzed with respect to causes and incidence of types and to age and sex incidence. They were divided into two main groups, namely, the infectious, consisting of 1,726 cases (36.9 per cent), and the noninfectious (Table I), consisting of 2,952 cases (63.1 per cent). Relatively, the cases of noninfectious heart disease increased from 55 per cent to 63.1 per cent from the time the total number of cardiac deaths was 3,380, about ten years ago, to the end of 1938, when the number was 4,678 cases.

I. INFECTIOUS HEART DISEASE

The infectious group comprises those classed as (*A*) rheumatic, (*B*) bacterial, (*C*) syphilitic, and (*D*) "toxic myocardium" (Table I).

A. Rheumatic Heart Disease includes the kind of valvulitis immediately associated with acute rheumatic fever or chorea, the different kinds of valve deformities, and the cases in which death resulted entirely or primarily from an adherent pericardium.

In acute and recurrent rheumatic endocarditis there is acute infection, with active valvulitis and vegetations. In the recurrent type there are acute verrucous vegetations on valves which grossly show previous thickening. The various kinds of valve deformities are caused by repeated attacks of rheumatic proliferative inflammation.

There were 870 cases of rheumatic heart disease in the entire group. This was 50.4 per cent of the infectious group and 18.6 per cent of the entire 4,678 cases. The rheumatic group (Table I) was divided into (*1*) acute rheumatic endocarditis, ninety-eight cases (11.3 per cent of rheumatic group and 2.1 per cent of total), (*2*) recurrent rheumatic endocarditis, eighty-five cases (9.8 per cent of rheumatic and 1.8 per cent of total), (*3*) valve deformities, 650 cases (74.7 per cent of rheumatic and 13.9 per cent of total), and (*4*) adherent pericardium, thirty-seven cases (4.2 per cent of rheumatic and 0.8 per cent of total). There

TABLE I

CARDIAC DISEASES (4,678 CASES)

TYPES	PERCENTAGE OF GROUPS			PERCENTAGE OF TOTAL GROUP			
I. Infectious (1,726)				36.9			
A. Rheumatic (870)	50.4				18.6		
1. Acute rheumatic (98)		11.3				2.1	
2. Recurrent rheumatic (85)		9.8				1.8	
3. Valve deformities (650)		74.7				13.9	
a. Incompletely healed Class I (125)			19.2				2.7
b. Completely healed Class II (265)			40.8				5.7
c. Calcific nodular aortic Class III (260)			40.0				5.5
4. Adherent pericardium (37)		4.2				0.8	
B. Bacterial (514)	29.8				11.0		
1. Primary acute (49)		9.5				1.0	
2. Secondary acute (101)		19.6				2.2	
3. Subacute (364)		70.8				7.8	
C. Syphilitic (327)	18.9				7.0		
1. Aortic insufficiency (180)		55.0				3.8	
2. Narrowing of coronary orifices (74)		22.6				1.6	
3. Rupture of aortic aneurysm (68)		20.8				1.5	
4. Gumma of myocardium (5)		1.5				0.1	
D. Toxic myocardium (15)	0.9				0.3		
II. Noninfectious (2,952)				63.1			
A. Hypertensive, primary (2,597)	88.0				55.5		
1. Myocardial insufficiency (1,124)		43.3				24.0	
a. B.P. 150 or more (747)			66.6				16.0
b. B.P. below 150; heart weight, M 500 or more; F 450 or more (149)			13.3				3.0
c. B.P. unknown; heart weight as in (b) (163)			14.5				3.6
d. B.P. unknown; heart weight M below 500; F, below 450 (65)			5.8				1.3
2. Coronary sclerosis (935)		36.0				20.0	
a. B.P. 150 or more (285)			30.5				6.1
b. B.P. below 150 or unknown; heart weight M 500 or more; F 450 or more (290)			31.0				6.2
c. B.P. as in *b;* heart weight M 400-499; F 350-449 (360)			38.5				7.6
3. Encephalopathy (apoplexy) (362)		13.9				7.7	
a. B.P. 150 or more (296)			81.8				6.3
b. B.P. low or unknown; heart weight M 500 or more; F 450 or more (66)			18.2				1.4
4. Renal insufficiency (176)		6.8				3.8	
B. Coronary sclerosis; B.P. below 150; heart weight M below 400; F below 350 (280)	9.5				6.2		
C. Pulmonary hypertension (69)	2.3				1.5		
D. Miscellaneous (6)	0.2						
1. Thyroid heart (6)		100.0					
a. Hyperthyroid (5)			83.4				
b. Hypothyroid (1)			16.6				
2. Primary renal disease							
a. Glomerulonephritis (0)							
3. Beriberi heart (0)		0.0	0.0				
4. Cardiac hypertrophy and dilatation without hypertension		?					

were three classes of valve deformities (Table I), namely (*a*) the incompletely healed valve deformities, 125 cases (19.2 per cent of valve deformities and 2.7 per cent of total), (*b*) the completely healed valve deformities, 265 cases (40.8 per cent of valve deformities and 5.7 per cent of total), and (*c*) the calcific, nodular, aortic valve deformity, 260 cases (40 per cent of valve deformities and 5.5 per cent of total). Classes *a* and *b* might as well be considered together, for microscopic examination shows that some degree of activity is common to most of the valve deformities. Class *c* is regarded by some observers as not of rheumatic origin. We have analyzed this group previously, and have failed to find any reason why it should not be classed as rheumatic. Structurally, the calcific, nodular, aortic valve deformity cannot be differentiated from calcific mitral lesions. If the calcific aortic valve deformity is not of rheumatic origin, one would have to conclude that the aortic valve is seldom infected with the rheumatic infectious agent. The calcific, nodular type of lesion is the one usually seen as a non-syphilitic aortic valve deformity.

Age and Sex (Table II). Acute rheumatic endocarditis is primarily a disease of young persons. Thirty-two of the forty-eight males (66.7 per cent) and thirty-one of the fifty females (62 per cent) died in the first two decades. Seven males and fourteen females died in the third and fourth decades. Only nine of the forty-eight males and five of the fifty females died in decades above the fourth. In a large series of autopsies over a period of several years, acute rheumatic endocarditis is seldom found in older persons, but in our series of ninety-eight cases one man and two women died in the ninth and tenth decades.

The number of each sex who died of the various types of heart disease was compared with the total number of respective male or female autopsies from which the cardiac cases were taken during the same period. This method gave a more nearly correct percentage, or rate per thousand, of autopsies, and probably of the general population, than the percentage of the total number of cases which occurred in each sex in each type, for, in the upper decades, more autopsies were performed on men than on women. There were 19,685 autopsies on males and 10,580 on females. In comparing the proportion of the sex incidence, the number per thousand (M) rather than the percentage (%) was used for the purpose of making the difference more apparent.

In the acute rheumatic group there were 2.4 males per thousand and 4.7 females per thousand, or about two females to one male. This is a significant difference. In only one of the decades, the third, was the difference significant, i.e., 2.3 males per thousand and 8.5 females per thousand.

In cases of recurrent rheumatic endocarditis death occurred somewhat later than from acute rheumatic endocarditis. The greatest number of males per decade was in the second and fourth, and, of females,

TABLE II

AGE AND SEX INCIDENCE IN TYPES OF RHEUMATIC HEART DISEASE (870 CASES)

DECADE	AUTOPSIES	A.R.		R.R.		VD "a"		VD "b"		VD "c"		AD. PER.		TOTAL	
		NO.	M	NO.	M	NO.	M	NO.	M	NO.	M	NO.	M	NO.	M
Males (522 Cases)															
1	2,978	15	5.0	0	0.0	1	0.3	0	0.0	0	0.0	3	1.0	19	6.4*
2	645	17	26.3	9	13.9	1	1.5	2	3.1	2	3.1	6	9.3	37	57.3
3	1,324	3	2.3*	8	6.0	8	6.0	16	12.1	8	6.0	6	4.5*	49	37.0
4	2,052	4	1.9	9	4.4	11	5.4*	27	13.1	26	12.7*	3	1.5	80	39.0
5	3,132	1	0.3	6	1.9*	23	7.3	40	12.8*	40	12.8*	5	1.6	115	36.7*
6	3,439	3	0.9	6	1.7	14	4.1	22	6.4*	47	13.7*	3	0.9	95	27.6*
7	3,350	3	0.9	2	0.6	4	1.2*	8	2.4*	45	13.4*	0	0.0	62	18.5
8	2,172	1	0.5	1	0.5	5	2.3	6	2.8	42	19.3*	2	0.9	57	26.2
9	565	1	1.8	0	0.0	1	1.8	2	3.5	4	7.1	0	0.0	8	14.2
10	28	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	19,685	48	2.4*	41	2.1*	68	3.4*	123	6.2*	214	10.9*	28	1.4	522	26.5*
Females (348 Cases)															
1	2,208	16	7.2	4	1.8	1	0.4	2	0.9	0	0.0	0	0.0	23	10.4*
2	574	15	26.1	13	22.6	1	1.7	4	7.0	1	1.7	3	5.2	37	64.5
3	1,174	10	8.5*	6	5.1	5	4.2	19	16.2	4	3.4	1	0.8*	45	38.3
4	1,283	4	3.1	5	3.9	14	10.9*	23	18.0	3	2.3*	0	0.0	49	38.2
5	1,347	1	0.7	10	7.4*	14	10.4	39	28.9*	5	3.7*	2	1.5	71	52.7*
6	1,411	0	0.0	4	2.8	11	7.8	30	21.3*	11	7.8*	2	1.4	58	41.1*
7	1,342	1	0.7	1	0.7	7	5.2*	17	12.7*	9	6.7*	0	0.0	35	26.1
8	930	0	0.0	1	1.1	4	4.3	6	6.4	7	7.5*	1	1.1	19	20.4
9	279	2	7.2	0	0.0	0	0.0	2	7.2	5	18.0	0	0.0	9	32.2
10	32	1	31.2	0	0.0	0	0.0	0	0.0	1	31.2	0	0.0	2	62.5
Total	10,580	50	4.7*	44	4.1*	57	5.4*	142	13.4*	46	4.3*	9	0.8	348	32.9*

*A significant difference.

in the second, but it is to be noted that the number was relatively large from the second to the sixth for the males (thirty-eight, or 92.7 per cent) and from the second to the fifth for the females (thirty-four, or 77.3 per cent).

In the recurrent rheumatic cases, as in the acute rheumatic group, the females outnumbered the males. There were 2.1 males per thousand autopsies on males, and 4.1 females per thousand autopsies on females. The only decade in which there was a significant sex difference was the fifth, in which there were 1.9 males per thousand and 7.4 females per thousand.

In the group of incompletely healed valve deformities (*a*) the greatest number of males per decade was in the fifth and of females in the fourth and fifth. Forty-eight of the sixty-eight males (70.6 per cent) and thirty-nine of the fifty-seven females (68.4 per cent) died in the fourth, fifth, and sixth decades.

In this group, also, there were more females than males (3.4 males per thousand and 5.4 females per thousand, which is a significant difference). A significant sex difference was noted in the fourth decade (5.4 males per thousand and 10.9 females per thousand). In the second division of valve deformities (*b*), those with completely healed valves, the greatest number per decade in both sexes died in the fifth, which is about the same as in division *a*. One hundred thirteen of the 123 males (91.8 per cent) and 128 of the 142 females (90.1 per cent) in the valve deformities group (*b*) died in the third, fourth, fifth, sixth, and seventh decades.

In this second class (*b*) of valve deformities there were 6.2 males per thousand autopsies on males, and 13.4 females per thousand autopsies on females, which is a significant difference. There was also a significant sex difference in three of the decades, namely, the fifth (12.8 males and 28.9 females per thousand), the sixth (6.4 males and 21.3 females per thousand), and the seventh (2.4 males and 12.7 females per thousand).

In the calcific, nodular, aortic valve deformity class (*c*), the greatest number of deaths per decade in both sexes occurred in the sixth. Two hundred of the 214 males (93.7 per cent) died in the fourth, fifth, sixth, seventh, and eighth decades, and thirty-seven of the forty-six females (80.4 per cent) in the fifth, sixth, seventh, eighth, and ninth decades. It is evident that persons in this group live longer than those in the two preceding classes.

Contrary to what was found in classes *a* and *b*, in class *c* the males greatly outnumbered the females. There were 10.9 males per thousand autopsies on males, and 4.3 females per thousand autopsies on females, which is a definite, significant difference. There was also a significant sex difference in five of the decades, namely, the fourth (12.7 males and 2.3 females per thousand), the fifth (12.8 males and 3.7 females per thousand), the sixth (13.7 males and 7.8 females per thousand),

the seventh (13.4 males and 6.7 females per thousand), and the eighth (19.3 males and 7.5 females per thousand).

In the thirty-seven cases in which death was caused by an adherent pericardium, the greatest number of males per decade died in the second and third decades. The highest per decade for the females was in the second. In this group there were 1.4 males per thousand autopsies on males, and 0.8 females per thousand autopsies on females. This difference was not significant. There was probably a significant sex difference in the third decade (4.5 males and 0.8 females per thousand).

In the entire rheumatic group of 870 cases, the greatest number per decade in both sexes was in the fifth.

There was probably a significant sex difference (26.5 males and 32.9 females per thousand autopsies), but this difference of 6.4 per thousand was relatively small. A probably significant sex difference in the total rheumatic group was noted in three decades, namely, the first (6.3 males and 10.4 females per thousand), the fifth (36.7 males and 52.7 females per thousand), and sixth (27.6 males and 41.1 females per thousand).

B. Bacterial Endocarditis may be similar etiologically to acute or recurrent rheumatic endocarditis, but since the bacterial type runs a different clinical course and shows different clinical manifestations, the diseases should be considered as separate entities. Patients with bacterial endocarditis develop a secondary anemia, have embolic processes in the spleen, kidneys, brain, lungs, and intestines, run a septic course, and die, as a rule, within less than two years. The microscopic structural inflammatory reaction within the valves is similar to that in the valves in acute rheumatic endocarditis, but the vegetations are larger and soft, and, as a rule, contain many colonies of bacteria. This large, heavily infected vegetation, we believe, accounts for the clinical and anatomic differences between acute rheumatic endocarditis and bacterial endocarditis.

There were 514 cases of bacterial endocarditis (29.8 per cent of the infectious cases and 11 per cent of the total). On clinical grounds, the cases of bacterial endocarditis were divided into three classes, namely, (*1*) primary acute bacterial endocarditis, in which death occurred within less than six weeks after the beginning of symptoms, forty-nine cases (9.5 per cent of the bacterial and 1.0 per cent of the total), (*2*) secondary acute bacterial endocarditis, in which there was some other infection or some wasting disease, 101 cases (19.6 per cent of the bacterial and 2.2 per cent of the total), and (*3*) subacute bacterial endocarditis, in which the symptoms had lasted more than six weeks, 364 cases (70.8 per cent of the bacterial and 7.8 per cent of the total). The two acute classes differ to some extent from the subacute class. The organism usually found in the blood of patients with subacute bacterial endocarditis is the *Streptococcus viridans. Streptococcus hemolyti-*

cus, Staphylococcus aureus, and the gonococcus are more commonly found in the clinically acute types.

Age and Sex (Table III).—The greatest number of males per decade in the group of cases of primary acute bacterial endocarditis died in the fifth decade, and the greatest number of females in the fourth. In both sexes the majority of deaths occurred in the earlier decades.

TABLE III

AGE AND SEX INCIDENCE IN TYPES OF BACTERIAL ENDOCARDITIS (514 CASES)

DECADE	AUTOPSIES	PRIMARY ACUTE		SECONDARY ACUTE		SUBACUTE		TOTAL	
		NO.	M	NO.	M	NO.	M	NO.	M
Males (312 Cases)									
1	2,978	1	0.3	1	0.3	3	1.0	5	1.7
2	645	3	4.6	1	1.5	13	20.1*	17	26.3*
3	1,324	3	2.3	6	4.5*	45	34.0	54	40.8
4	2,052	3	1.5*	11	5.4*	53	25.6	67	32.6
5	3,132	8	2.5	8	2.5	53	17.0	69	22.0
6	3,439	2	0.6	10	2.9	39	11.3*	51	14.8
7	3,350	4	1.2	8	2.4	27	8.1*	39	11.6
8	2,172	1	0.5	3	1.4	2	0.9	6	2.8
9	565	0	0.0	2	3.5	2	3.5	4	7.1
10	28	0	0.0	0	0.0	0	0.0	0	0.0
Total	19,685	25	1.3*	50	2.5*	237	12.0	312	15.8*
Females (202 Cases)									
1	2,208	2	0.9	2	0.9	3	1.3	7	3.2
2	574	4	7.0	2	3.5	22	38.3*	28	48.8*
3	1,174	5	4.2	16	13.6*	38	32.4	59	50.2
4	1,283	8	6.2*	14	10.9*	28	21.8	50	40.0
5	1,347	0	0.0	5	3.7	18	13.4	23	17.1
6	1,411	1	0.7	7	5.0	9	6.4*	17	12.0
7	1,342	2	1.5	4	3.0	6	4.5*	12	8.9
8	930	2	2.1	0	0.0	2	2.1	4	4.3
9	279	0	0.0	1	3.6	1	3.6	2	7.2
10	32	0	0.0	0	0.0	0	0.0	0	0.0
Total	10,580	24	2.3*	51	4.8*	127	12.0	202	19.1*

*A significant difference.

In this group the females predominated (1.3 males and 2.3 females per thousand autopsies). The outstanding and significant sex difference was in the fourth decade (1.5 males and 6.2 females per thousand autopsies).

In the group of cases of secondary bacterial endocarditis the majority of deaths in both sexes occurred in the earlier decades. The greatest number of males per decade was in the fourth, and, of the females, in the third.

As in the preceding group, the females outnumbered the males (2.5 males and 4.8 females per thousand autopsies). The greatest difference was in the third decade (males 4.5 and females 13.6 per thousand autopsies). The next greatest sex difference was found in the fourth decade (5.4 males and 10.9 females per thousand autopsies). In the total and in both of these decades the sex differences were significant.

In the 364 cases of subacute bacterial endocarditis, the greatest number of males per decade died in the fourth and fifth, and the greatest number of females in the third. Death occurred earlier in the females.

The sex incidence in the entire group was the same (twelve per thousand autopsies in both). There was a probably significant sex difference in three decades, namely, the second (20.1 males and 38.3 females per thousand autopsies), the sixth (11.3 males and 6.3 females per thousand autopsies), and the seventh (8.1 males and 4.5 females per thousand autopsies). It is to be noted that in the earlier decade, the second, the females predominated, and, in the later, the sixth and seventh, the males predominated.

In the entire group of 514 cases of bacterial endocarditis, acute and subacute, there was a significant sex difference (15.8 males and 19.1 females per thousand autopsies). A significant sex difference was noted in only one decade, the second (26.3 males and 48.7 females per thousand autopsies). The sex difference in the total number was due to the incorporation of the cases of primary and secondary acute endocarditis.

C. Syphilitic Heart Disease (Table IV).—The third group of cases of infectious heart disease are those of cardiac failure in which, except in one case, a gumma of the myocardium, syphilitic aortitis was present. There were 327 of these cases (18.9 per cent of the infectious heart disease and 7 per cent of the total).

Depending upon the manner in which death occurred, these syphilitic heart diseases fell into four groups: (*1*) aortic insufficiency caused by syphilitic valvulitis, 180 cases (55 per cent of the syphilitic cases and 3.8 per cent of the total); (*2*) narrowing of the coronary orifices, seventy-four cases (22.6 per cent of the syphilitic cases and 1.6 per cent of the total); (*3*) rupture of a syphilitic aneurysm, sixty-eight cases (20.8 per cent of the syphilitic cases and 1.5 per cent of the total); and (*4*) gumma of the myocardium, five cases (1.5 per cent of the syphilitic cases and 0.1 per cent of the total). There was a good deal of overlapping in the first three classes.

Age and Sex.—The greatest number of males with aortic insufficiency died in the sixth decade. The greatest number of the females died in the sixth and seventh decades. The majority of the males died in the fourth, fifth, sixth, and seventh decades, and the majority of females in the fifth, sixth, and seventh.

The males in this division greatly outnumbered the females (8.0 males and 2.2 females per thousand autopsies). The two decades in which there was a significant sex difference were the fifth (14.4 males and 4.5 females per thousand) and the sixth (18.3 males and 5.0 females per thousand).

In the group in which death was caused primarily by narrowing of the coronary orifices, the greatest number per decade in both sexes

occurred in the fourth. The majority in both sexes died in the fourth, fifth, sixth, and seventh decades.

There was a preponderance of males, but it was not so great as in the aortic insufficiency group (2.8 males and 1.7 females per thousand). A significant sex difference was noted in the fourth decade (6.3 males and 2.3 females per thousand).

TABLE IV

AGE AND SEX INCIDENCE IN TYPES OF SYPHILITIC HEART DISEASE (327 CASES)

DECADE	AUTOPSIES	SYPHILIS (A)		SYPHILIS (B)		SYPHILIS (C)		SYPHILIS (D)		TOTAL	
		NO.	M	NO.	M	NO.	M	NO.	M	NO.	M
Males (274 Cases)											
1	2,978	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	645	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
3	1,324	2	1.5	1	0.7	0	0.0	1	0.7	4	3.0
4	2,052	16	7.8	13	6.3*	4	1.9	1	0.5	34	16.6*
5	3,132	45	14.4*	25	8.0	21	6.7*	0	0.0	91	29.1*
6	3,439	63	18.3*	12	3.5	13	3.8	0	0.0	88	25.6*
7	3,350	29	8.6	5	1.5	17	5.1*	0	0.0	51	15.2*
8	2,172	1	0.5	0	0.0	4	1.8	0	0.0	5	2.3
9	565	1	1.8	0	0.0	0	0.0	0	0.0	1	1.8
10	28	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	19,685	157	8.0*	56	2.9*	59	3.0*	2	0.1	274	13.9*
Females (53 Cases)											
1	2,208	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	574	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
3	1,174	2	1.7	1	0.8	0	0.0	0	0.0	3	2.6
4	1,283	1	0.8	3	2.3*	0	0.0	2	1.5	6	4.7*
5	1,347	6	4.4*	7	5.2	2	1.5*	1	0.7	16	11.9*
6	1,411	7	5.0*	3	2.1	4	2.8	0	0.0	14	9.9*
7	1,342	7	5.2	3	2.2	3	2.2*	0	0.0	13	9.7*
8	930	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
9	279	0	0.0	1	3.6	0	0.0	0	0.0	1	3.6
10	32	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	10,580	23	2.2*	18	1.7*	9	0.8*	3	0.3	53	5.0*

*A significant difference.

In the cases in which death occurred mainly from rupture of a syphilitic aortic aneurysm, the greatest number of males per thousand was in the fifth decade, and females in the sixth. Most of the deaths in both sexes occurred in the fifth, sixth, and seventh decades.

The males predominated (3 males and 0.8 females per thousand). There were two decades in which a significant sex difference was noted, namely, the fifth (6.7 males and 1.5 females per thousand) and the seventh (5.1 males and 2.2 females per thousand).

There were only five cases of syphilitic cardiac disease in which death was caused by gumma of the myocardium (two males and three females). The males died in the third and fourth decades, and the females in the fourth and fifth.

D. Toxic Myocardium.—Death from toxic myocardium, the fourth group of cases of infectious cardiac disease, was rare. This group was

included with the cases of infectious disease because the lesion, in this series, generally resulted from the effect of diphtheria toxin upon the heart muscle. There were fifteen cases (0.9 per cent of the infectious cases and 0.3 per cent of the total).

II. NONINFECTIOUS HEART DISEASES

The noninfectious cardiac diseases (Table II) caused most of the cardiac failure in this series. The percentage of this group has increased from 55 per cent to 63 per cent in the autopsy material in the last ten years. There were 2,952 cases (63.1 per cent of the total cardiac deaths) in the noninfectious heart disease group.

This group of 2,952 cases was composed of (*A*) hypertensive heart disease, (*B*) coronary sclerosis without hypertension, (*C*) pulmonary hypertensive heart disease, and (*D*) miscellaneous forms, such as heart disease associated with (*a*) hyperthyroidism or (*b*) hypothyroidism (Table I).

A. Hypertensive Heart Disease.—This large group includes the cases in which death was brought about by the effects of high blood pressure, primarily on the heart muscle. Cardiac hypertrophy and dilatation were usually present in these cases, but many of the patients died from coronary sclerosis, cerebral hemorrhage, or uremia. These cases have been classed as cardiac hypertrophy and dilatation, and chronic myocarditis, but, since in the majority there was an intimately associated hypertension, it seems preferable to classify them as cases of hypertensive heart disease. There were 2,597 cases (88 per cent of the noninfectious cases and 55.5 per cent of the total).

Depending upon the manner in which death occurred, the group has been divided into four divisions: (*1*) myocardial insufficiency, (*2*) coronary sclerosis with hypertension, (*3*) encephalopathy (apoplexy), and (*4*) renal insufficiency.

1. Myocardial Insufficiency.—In these cases, with few exceptions, there were hypertrophy and dilatation of the heart and congestive failure. There were 1,124 cases (43 per cent of the hypertensive group and 24 per cent of the total). The 1,124 cases were classed as hypertensive heart disease on the basis of a history of elevation of the blood pressure and upon the weight of the heart. A few cases in which there were congestive heart failure, but small hearts and no record of increased blood pressure, were also grouped with the hypertensive cases. A systolic blood pressure of 150 mm. Hg, or more, was taken to mean hypertension. There were 747 cases in which this required reading occurred. Male hearts which weighed 500 Gm. or more, and female hearts of 450 Gm. or more, in the absence of valve deformities or an adherent pericardium, were considered to be hypertensive hearts. In this group there were 149 cases (13.3 per cent of the myocardial in-

sufficiency group and 3 per cent of the total) in which the systolic pressure was known to have been below 150 mm. Hg, and 163 cases (14.5 per cent of the myocardial insufficiency group and 3.6 per cent of the total) in which the blood pressure was unknown. Hearts with hypertrophy in cases of glomerulonephritis were not included. There was a small group with heart weights below the above requirement (sixty-five cases, or 5.8 per cent of the cases of myocardial insufficiency and 1.3 per cent of the total). These patients had had cardiac dilatation and general congestive failure. Most of them had some degree of hypertrophy.

Age and Sex (*Table V*).—In the group of patients with myocardial insufficiency, the greatest number died in the seventh decade. A large majority of the deaths occurred in the fifth to ninth decades in both sexes. No deaths occurred in the first two decades among the males and in the first three decades among the females.

TABLE V

AGE AND SEX INCIDENCE IN TYPES OF HYPERTENSIVE HEART DISEASE (2,597 CASES)

DECADE	AUTOPSIES	HYPERTENSION I		HYPERTENSION II		HYPERTENSION III		HYPERTENSION IV		TOTAL	
		NO.	M	NO.	M	NO.	M	NO.	M	NO.	M
Males (1,881 Cases)											
1	2,978	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	645	0	0.0	0	0.0	0	0.0	2	3.1	2	3.1
3	1,324	6	4.5	1	7.5	3	2.3	1	0.7	11	8.3
4	2,052	27	13.2	12	5.8*	10	4.9	9	4.4*	58	28.3*
5	3,132	99	31.6	104	33.2*	37	11.8*	29	9.2	269	85.9*
6	3,439	218	63.4	190	55.2*	79	23.0	28	8.1	515	149.8*
7	3,350	234	69.8	263	75.5*	66	19.7	26	7.8	589	175.8*
8	2,172	173	79.6	135	62.1*	34	15.6	7	3.2	349	160.7
9	565	39	69.0	41	72.6*	3	5.4	3	5.3	86	152.2
10	28	2	71.4	0	0.0	0	0.0	0	0.0	2	71.4
Total	19,685	798	40.5*	746	37.9*	232	11.8	105	5.3	1,881	95.6*
Females (716 Cases)											
1	2,208	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	574	0	0.0	0	0.0	2	3.5	5	8.7	7	12.2
3	1,174	0	0.0	0	0.0	3	2.5	3	2.5	6	5.1
4	1,283	18	15.6	3	2.3*	10	7.8	18	14.0*	49	38.2*
5	1,347	39	28.7	6	4.4*	31	23.0*	18	13.5	94	69.8*
6	1,411	80	56.7	31	22.0*	30	21.2	12	8.5	153	108.4*
7	1,342	94	70.0	69	51.4*	31	23.1	7	5.2	201	149.8*
8	930	70	75.3	69	73.1*	15	16.1	6	6.4	160	172.0
9	279	25	89.4	11	39.4*	7	25.1	1	3.6	44	157.7
10	32	0	0.0	0	0.0	1	31.1	1	31.2	2	62.5
Total	10,580	326	30.8*	189	17.8*	130	12.3	71	6.7	716	67.7*

*A significant difference.

There was a significant sex difference in the total group of 1,124 cases (40.5 males and 30.8 females per thousand autopsies). No significant sex difference existed in any of the decades in this group.

2. Coronary Sclerosis With Hypertension.—The second group of cases of cardiac disease with hypertension were those in which death was due primarily to coronary sclerosis or to sclerosis and thrombosis. There were 935 cases (36 per cent of the hypertensive group and 20 per cent of the total).

On the basis of the evidence of hypertension, three groups of the cases of coronary disease were recognized: those in which there was a systolic blood pressure of 150 mm. Hg or more, 285 cases (30.5 per cent of the hypertensive coronary group and 6.1 per cent of the total); those in which the systolic blood pressure was below 150 mm. Hg, or the blood pressure was unknown, and in which the male heart weights were 500 Gm. or more, and the female, 450 Gm. or more, 290 cases (31 per cent of the hypertensive coronary cases and 6.2 per cent of the total); and those in which the systolic blood pressure was below 150 mm. Hg, or was unknown, and in which the male heart weights were 400 to 499 Gm., and the female, 350 to 449 Gm. Some in this third division may have been questionably hypertensive cases, but probably in most of them, especially those in which the heart weights were greater, there was a degree of hypertrophy most like that caused by hypertension. In this division of hypertensive coronary sclerosis there were 360 cases (38.5 per cent of the hypertensive coronary sclerosis cases and 7.6 per cent of the total).

Age and Sex (Table V).—The greatest number of males in the cases of hypertensive coronary sclerosis died in the seventh decade, and, of the females, in the seventh and eighth decades. The majority of the males were in the fifth to eighth decades and the females in the sixth to ninth decades. The males greatly outnumbered the females in the total number of 935 cases (37.9 males per thousand autopsies on males and 17.8 females per thousand autopsies on females). There was a significant male predominance in all the decades in which death occurred except in the third, in which there was only one death, a male. The greatest sex difference was in the fifth decade (33.2 males and 4.4 females per thousand autopsies).

3. Encephalopathy (Apoplexy).—The third division of the hypertensive cases included those in which death was caused by cerebral hemorrhage. In most of these there were also evidences of cardiac failure, both clinically and at autopsy. Death evidently would probably have resulted from cardiac failure had life not been terminated by hemorrhage of the brain.

In this apoplectic group there were 362 cases (13.9 per cent of the hypertensive group and 7.7 per cent of the total). By our method of determining the presence of hypertension, this apoplectic group was divided into two subgroups. In the first (296 cases, or 81.8 per cent of the encephalopathy group and 6.3 per cent of the total) the recorded blood pressure was 150 mm. Hg or more. Those in the second, consisting

of sixty-six cases (18.2 per cent of the encephalopathy cases and 1.4 per cent of the total), were classed as hypertensive cases because the male hearts all weighed 500 Gm. or more, and the female hearts, 450 Gm. or more. It is probable that some cases of cerebral hemorrhage in which the blood pressure was less than 150 mm. Hg and the hearts weighed less than 500 Gm. in males and 450 Gm. in females should be included in this group, but they were not because it could not be determined with certainty that hypertension had existed.

Age and Sex (Table V).—The greatest number of males died in the sixth decade, and, of the females, in the fifth and seventh. A large majority of the deaths in both sexes occurred in the fifth to eighth decades. In the entire number there was no significant sex difference, but in the fifth decade there was a preponderance of females (11.8 males and 23 females per thousand autopsies).

4. Renal Insufficiency.—The fourth group of hypertensive cases was composed of those in which, although as a rule there were signs of cardiac failure, death was caused by uremia. Death would likely have been cardiac had uremia not intervened. In all of these there was a systolic blood pressure of 150 mm. Hg or more, or a male heart weight of at least 500 Gm. or a female heart weight of at least 450 Gm. There were 176 renal cases (6.8 per cent of the hypertensive group and 3.8 per cent of the total).

Age and Sex (Table V).—Most of the deaths in both sexes occurred in the fourth, fifth, sixth, and seventh decades. There were two males and five females in the second decade, and one male and three females in the third decade.

The sexes were about equal (5.3 males and 6.7 females per thousand autopsies). A significant sex difference was noted in one decade, the fourth, in which the females outnumbered the males (4.4 males and 14.0 females per thousand autopsies).

B. Coronary Sclerosis Without Hypertension.—The second group of noninfectious heart diseases was coronary sclerosis without hypertension. In all of these cases there was either a history of low blood pressure or the male hearts weighed less than 400 Gm., and the female hearts less than 350 Gm. There were 280 of these (9.5 per cent of the noninfectious cases and 6.2 per cent of the total). The total number of cases of coronary sclerosis in the entire cardiac group was 1,215. The 280 cases in which there was no hypertension constituted 23 per cent of the entire number of cases of coronary sclerosis. This indicates that in about 77 per cent of all cases of coronary sclerosis there is an associated hypertension.

Age and Sex (Table VI).—Most of the deaths in both sexes occurred in the fifth, sixth, seventh, and eighth decades. The males greatly outnumbered the females (12.6 males and 3 females per thousand

autopsies). In the entire group of cases of coronary sclerosis, with or without hypertension, the ratio of males to females was 2.5: 1 (males 50 per thousand and females 20 per thousand).

TABLE VI

AGE AND SEX INCIDENCE IN CORONARY SCLEROSIS WITHOUT HYPERTENSION (280 CASES)

DECADE	MALES (248 CASES)			FEMALES (32 CASES)		
	AUTOPSIES	NO.	M	AUTOPSIES	NO.	M
1	2,978	0	0.0	2,208	0	0.0
2	645	0	0.0	574	0	0.0
3	1,324	4	3.0	1,174	0	0.0
4	2,052	18	8.8*	1,283	1	0.8*
5	3,132	51	16.3*	1,347	5	3.7*
6	3,439	65	18.9*	1,411	6	4.2*
7	3,350	53	15.8*	1,342	6	4.5*
8	2,172	39	17.9*	930	9	9.7*
9	565	16	28.3	279	5	17.9
10	28	2	71.4	32	0	0.0
Total	19,685	248	12.6*	10,580	32	3.0*

*A significant difference.

C. Pulmonary Hypertension.—Primary, right-sided heart failure as a result of increased pressure in the pulmonary artery is not an uncommon condition. There were sixty-nine cases (2.3 per cent of the noninfectious cardiac cases and 1.5 per cent of the total) in this series. The cause of primary, right-sided heart failure, or cor pulmonale, is not a specific one. In the sixty-nine cases the causal factors, listed in order of their frequency, were as follows: pulmonary tuberculosis (sixteen), bronchial asthma (fifteen), bronchiectasis (nine), pulmonary arteriosclerosis (nine), chest deformity (five), pulmonary embolism or thrombosis (five), emphysema (three), silicosis (two), pressure of a syphilitic aneurysm of the aorta upon the pulmonary artery (one), and nonspecific pulmonary fibrosis (one).

Age and Sex.—Thirty-nine of the forty-two males (92.8 per cent) and twenty of the twenty-seven females (74 per cent) died in the fourth to seventh decades. The sexes were about equal (2.1 males and 2.5 females per thousand autopsies).

D. Miscellaneous Group of Cases of Cardiac Failure.—There were few cases in this group. The thyroid heart, or cardiac death caused directly by the effects of hyperthyroidism or hypothyroidism upon the myocardium, was rare in our material. There were five cases in which the cardiac hypertrophy, dilatation, and congestive failure appeared definitely to be the result of hyperthyroidism. One patient with myxedema died of typical congestive heart failure.

The heart in cases of chronic glomerulonephritis regularly undergoes hypertrophy and dilatation, and clinically there is evidence of cardiac failure. The final cause of death, however, is uremia. We have had no cases of glomerulonephritis with congestive heart failure without uremia.

No case of beriberi heart, in so far as could be ascertained, was found among the more than 30,000 autopsies.

Cardiac hypertrophy and dilatation without hypertension, in the absence of valve deformity, still remains a much discussed and doubtful condition. It occurs congenitally in children and may possibly be found in the adult. It appears doubtful whether we have any such cases. The stigmata of hypertension were so common in those of our cases in which the blood pressure was not found to be elevated that we prefer to leave the question, "Is there an adult idiopathic cardiac hypertrophy and dilatation?" open for further study. All such cases in this analysis are included in the hypertensive group with myocardial insufficiency.

DISCUSSION

In a series of 30,265 autopsies there were 4,678 cardiac deaths (15.45 per cent). Etiologically, these were classed as cases of rheumatic, bacterial, syphilitic, hypertensive, arteriosclerotic (coronary), pulmonary hypertensive (cor pulmonale), and thyroid (hyper- and hypo-) heart disease.

The rheumatic group, 870 cases, comprised 18.6 per cent of the entire number of cases. Of these 870 cases, ninety-eight (11.3 per cent) were cases of acute rheumatic endocarditis, eighty-five (9.8 per cent) were cases of recurrent rheumatic endocarditis, and 650 (74.7 per cent) were cases of healed or nearly healed valve deformities; thirty-seven patients (4.2 per cent) died from the effects of an adherent pericardium.

The number of rheumatic cases in which death occurred during an acute attack was small. Patients with the calcific aortic valve deformity lived the longest. Acute rheumatic endocarditis is a disease primarily of young persons.

The sexes were almost equally represented in the rheumatic group, i.e., 25.6 males and 32.9 females per thousand autopsies. This was true only in the group as a whole. In the early decades the females predominated, and, in the later decades, the males were greatly in excess.

The 514 cases of bacterial endocarditis constituted 11 per cent of the entire cardiac group. In forty-nine of the 514 (9.5 per cent), the duration of symptoms was less than six weeks, and these were classed as cases of primary acute bacterial endocarditis. In 101 (19.6 per cent), the symptoms were the same as in the cases of primary acute endocarditis, but were secondary to some infection or wasting disease, and these cases were therefore classed as secondary acute bacterial endocarditis. In 364 of the 514 cases (70.8 per cent), the symptoms had lasted for more than six weeks, and these were classed as cases of subacute bacterial endocarditis.

In the combined group the greatest number of males died in the fifth decade, and the greatest number of females in the third. In the two

groups of acute endocarditis, the females predominated with a ratio of nearly 2:1. In the cases of subacute endocarditis the number was equal (twelve each per thousand autopsies). A factor in the sex difference in the cases of secondary acute endocarditis was the relatively large number of cases of abortion which were included. It is possible that among the cases of primary acute endocarditis there may have been some undetected abortions. The subacute endocarditis, as a rule, was caused by the *Streptococcus viridans*, whereas the organisms most frequently found in the acute cases were *Streptococcus hemolyticus* and *Staphylococcus aureus*.

There were 327 cases (7.0 per cent) of syphilitic cardiac disease in the entire series of 4,678 heart cases. In 180 (55 per cent), death occurred from aortic insufficiency; in seventy-four (22.6 per cent), from narrowing of the coronary orifices; in 68 (20.8 per cent), from rupture of an aortic aneurysm; and, in 5 (1.5 per cent), from gumma of the myocardium.

The majority of deaths occurred in the fourth, fifth, and sixth decades. The males predominated in the entire group, with a ratio of 2.8:1. The greatest preponderance of males was in the aortic insufficiency group (3.6:1).

Hypertension was by far the most frequent cause of cardiac disease. Of the total of 4,678, 2,597 (55.5 per cent) were hypertensive cases. In 1,124 (43.3 per cent) of these 2,597 cases, death was caused by myocardial insufficiency; in 935 (36 per cent) by coronary sclerosis; in 362 (13.9 per cent), by cerebral hemorrhage; and, in 176 (6.8 per cent), by renal insufficiency. In most cases, cardiac hypertrophy and dilatation were also present in the last two groups.

In all of the cases of hypertension, death occurred usually in the later decades, i.e., the fifth, sixth, seventh, eighth, and ninth. Males predominated among the patients who died of myocardial insufficiency (1.3:1) and coronary sclerosis (2.1:1). No significant sex difference was noted in the apoplectic and renal insufficiency groups.

There were 280 cases (9.5 per cent) of coronary sclerosis without hypertension. The total number of cases of coronary sclerosis with hypertension (935) and without hypertension (280) was 1,215 (25.9 per cent of all cardiac deaths). The males in the cases of coronary sclerosis without hypertension predominated with a greater ratio (4.2:1) than in those with hypertension.

Coronary sclerosis and the calcific nodular aortic valve deformity groups were the two outstanding divisions of heart disease in which there was a marked male preponderance. In the aortic stenosis group, this is explained by the fact that the aortic valve is involved more commonly in males than in females. The reason for the preponderance of males in the cases of death from coronary disease is not apparent.

Primary right-sided heart failure (cor pulmonale) was caused by a variety of conditions, and was distributed about equally between the two sexes.

Cardiac death from hyperthyroidism or hypothyroidism, without any other cardiac disease, was rare in this series of autopsies.

SUMMARY

A total of 4,678 cardiac deaths in a series of 30,265 autopsies (15.45 per cent) was analyzed. The incidence of the types, with the age and sex distribution, is given.

A classification of heart disease based upon etiology and autopsy observations is presented.

The statistical determinations were performed by Alice Marie Moeglein, M.S.

REFERENCE

1. White, P. D.: Heart Disease, New York, 1937, The Macmillan Co., p. 171.

THE NORMAL ELECTROCARDIOGRAM

I. Analysis of the Extremity Derivations From 100 Normal Persons Whose Ages Ranged From 30 to 50 Years

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UNTIL a few years ago, there was only one comprehensive work on the normal electrocardiogram, namely, that of Lewis and Gilder[16] (1912), in which an account is given of the appearance of the extremity derivations from fifty-two normal men whose ages ranged from 18 to 35 years. It seems, however, as if it was realized in several quarters about simultaneously that a series of only fifty-two normal subjects is insufficient, in view of the present scope of clinical electrocardiography. The result was a number of studies on the normal electrocardiogram, among which the following may be mentioned: Jensen, Smith and Cardwright,[11] Gross,[8] Hadorn,[9] Shipley and Hallaran,[22] Benedetti and Sabena,[2] Schulz,[21] Chamberlain and Hay,[3] Warnecke,[25] and Jenner, Hoskin, and Jonescu.[10] In addition, several papers have been published on questions of details, some of which will be cited occasionally in the following.

When, notwithstanding the appearance of these modern studies, we believe we are still able to offer an additional contribution concerning the normal electrocardiogram, it is largely for the following two reasons. On going through the above-mentioned publications it is found that most of the experimental subjects were very young persons, or, in a couple of the studies, elderly, i.e., persons over 50, whereas the age class from 30 to 50 years is poorly represented. And we believe that this very age class is of particular interest, for it is between the ages of 30 and 50 years that the degenerative heart lesions commence to assert themselves. In the next place, it is found that, in contrast to Lewis and Gilder, the more modern investigators have given an insufficient account of the suitability of the apparatus for the tracing of the electrocardiogram. It is to be emphasized that, even though the employment of amplifiers means an advance, these apparatuses are encumbered with just as many possibilities of error as the string galvanometers, although of a different nature. From the following—under "Technique"—it will be evident how thoroughly and comprehensively the apparatus itself ought to be examined.

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EXPERIMENTAL SUBJECTS

Our material comprised 100 normal persons whose ages were between 30 and 50 years; twenty-five men and twenty-five women were between 30 and 40, and 25 men and twenty-five women were between 40 and 50. The average ages for the four groups were 34.7, 35.0, 44.0, and 43.8 years, respectively. Of the women, forty-one were nurses in the Rigshospital, and nine were hospitalized patients. Of the men, seven were physicians, twenty-one were functionaries at the Rigshospital or similar institutions, and the rest were hospitalized patients. Of the patients here employed as "normal" subjects, seventeen were under treatment in Department B (lumbago-sciatica, seven patients; dyspepsia or gastroduodenitis, eight patients; omarthritis, one patient; sequelae of phlebitis, one patient), nine patients were in the Surgical Department C (fracture of the leg, four; hernia, two; lipoma, two; contusion of the face, one), and five patients were from Department H (eczema of slight degree, three; erythrasma, one; psoriasis of slight degree, one).*

All of the experimental subjects stated that they were able to stand physical exertion (work, sport) without having circulatory symptoms. None of them had ever had rheumatic diseases, but ten had had a mild attack of scarlet fever, and eight, a mild attack of diphtheria, many years earlier. Ordinary physical examination revealed no abnormality in any of them. As to their weight, most of them came very near the average given for their respective sex, age, and height in the weight tables of the Hafnia Insurance Co. In a couple of the cases the weight was 16 to 18 per cent above average. In all 100 subjects, roentgenographic examination of the chest showed that the heart was normal in shape and size, and that the lungs were normal. In all subjects the systolic blood pressure was less than 150 mm. mercury, and the diastolic, less than 100 mm. The sedimentation rate of the erythrocytes (in one hour) did not exceed 8 mm. for the men and 12 mm. for the women. The hemoglobin per cent was at least 85 (100 per cent = 18.5 volumes per cent of oxygen). The blood Wassermann reaction was negative on the hospitalized patients, and not done on the other subjects.

The subjects were selected solely on the basis of their anamnestic data. Because of the results of the objective examinations, a few subjects had to be excluded, namely, three for anemia, two for increased sedimentation rate, one for increased blood pressure, and two for adiposity. In the subject with increased blood pressure, the electrocardiogram showed left preponderance, and in one of the subjects with adiposity the electrocardiogram showed left preponderance and a QRS complex lasting 0.114 sec. In the other cases the electrocardiograms were normal. Finally, one subject, a nervous man, aged 32 years, was excluded because his heart rate during the tracing exceeded 100 per minute; in this case the S-T segment kept a level of 1 mm. below the isoelectric line in Leads II and S.

TECHNIQUE

The records were taken partly with derivation from the extremities, as used by Einthoven[5] (Leads I, II, and III), partly with the precordial derivations used by Groedel[7] (Leads *d* and *s*), and always with the subject in the reclining posture. The results of our studies on Leads *d* and *s* will appear in a subsequent paper.[23] The electrodes employed on the extremities, measuring about 70 sq. cm., were made of rust-proof steel, and covered with felt that was moistened in hot saline.

*We wish to acknowledge our indebtedness to the chiefs of Department C and Department H of the Rigshospital, Professor A. Lendorf and Professor H. Haxthausen, for permission to examine the patients from these departments. We likewise wish to give our best thanks to the chief of the X-Ray Clinic, Professor P. Flemming Moller, and his assistants, for the roentgenographic examination of our experimental subjects.

Most of the apparatus employed for the taking of the electrocardiogram was furnished by the Siemens and Halske A. G., and put together by Professor Warburg. In this apparatus the derived electrical potentials are amplified by two identical, four-stage, resistance-coupled amplifiers, with direct entrance to grid and earth, direct outlet to the oscillographic loops, and an entrance resistance of 1,000,000 ohms. With these amplifiers, Leads I and II are recorded simultaneously, and then Lead III is recorded with the same amplifier as Lead I. The tracing is made with bifilar oscillographic loops from Siemens and Halske A. G. The rate of movement of the photographic paper was 70 mm. per second. The time marking was done with a tuning fork and synchronizing motor from the Cambridge Scientific Instrument Co. Ltd., of London. On the shaft of the motor, which makes five revolutions per second, there is a disc with four slits, one of which is wider than the others, making the marked intervals 0.05 and 0.20 sec.

The suitability of the apparatus for the tracing of electrocardiograms was controlled frequently. The sensitivity of the amplifiers was controlled every day the apparatus was used; each derivation was supplied with a test pressure of 1 millivolt; the deflections for 1 mv. were about 20 mm. The capacity of the amplifiers for symmetrical tracing, true as to amplitude, and the accuracy of the timer were controlled about every twenty records. In all cases in which disproportionality and asymmetry gave rise to errors of more than 3 per cent in the height of the waves, corrections were made. The error from this source in the size of the various waves was, for waves up to 15 mm. in height (1.5 mv.), at the most, 0.5 mm.; and for waves up to 30 mm. in height, at the most, 1 mm. The timer was adjusted by tracing, on the film, the vibrations of a tuning-fork (a^1) which was checked in the Reichanstalt für physikalischen Messungen, Berlin, and found to have a period of 435 Hertz; the corrections, which were carried out invariably, never exceeded 2 per cent. Finally, through special tests, we have made sure that this apparatus, when it is used for electrocardiography, gives a record of the oscillations that is true as to frequency and phase. In making these tests, we ascertained the time constants of the two amplifiers, which, in both instances, were found to be 1.54 sec.; and, further, the damping constants and individual frequencies of the oscillographic loops were ascertained through analysis of individual charges sent directly through the loops. The latter examination, which was carried out by Professor Warburg, showed that the damping constants of the loops here employed were, respectively, 0.78 and 0.67, and that the individual frequencies of the two loops were, respectively, 870 and 820 Hertz.

In measuring the records, the isoelectric line was taken as a straight line that just touched the lower margin of the curve corresponding to the segments between the end of the U waves and the beginning of the P waves. The deviation of the P-Q segment from the isoelectric line was always measured at the point where the segment reached farthest down below, or farthest down towards, the isoelectric line. The deviation of the S-T segment from the isoelectric line was always measured at the point corresponding to 0.05 sec. after the end of the QRS complex. The size of the waves was measured from the inferior margin of the isoelectric line to the inferior margin of the curve at the apices of the waves. The measuring was done with calipers and a diagonal scale on six successive complexes in each derivation; the height of the waves was taken as the average of the six waves and converted to millivolts. The size of the waves was recorded in millimeters, so that 10 mm. $=$ 1 mv., which is the form of recording most commonly employed. In repeated readings on the same wave, the error of the reading has not exceeded ± 0.2 mm. (corresponding to about ± 0.1 mm. in the tabulated results). The duration of the various intervals was measured by means of calipers, and the time registered on the record, and given in seconds. Here, too, the measuring was carried out on six successive complexes

in each derivation. Because of the rapid rate at which the photographic paper traveled, it was possible to read the times within 0.005 sec.; this figure gives also the numerical value of the reading error in repeated measurements of the same interval.

On measuring the electrocardiograms it was found that the size of the waves and the length of the intervals varied a little from one complex to another. Generally, this variation is assumed to be due chiefly to changes in the position of the heart resulting from the respiratory movements. In order to get an idea about the correctness of the values given for the size of the waves and the length of the intervals, it was necessary, therefore, to know the dispersion on these values. These dispersions were not calculated for the present material, but are known from previous work in which one of us (K. L.) took and measured electrocardiograms on twenty normal, younger persons with the same technique as described above. G. Rasch, Ph.D., calculated the dispersions for some of the more important values in Lead II, and found them to be 0.55 mm. for the R wave, 0.31 mm. for the T wave, 0.004 sec. for the P-Q interval, 0.003 sec. for the QRS complex, and 0.005 sec. for the Q-T interval. The aforementioned reading errors are included, of course, in these values for the dispersions. A review of the measuring results shows that the dispersions in Lead I must be of the same magnitude as in Lead II, whereas the dispersions for the R wave and the T wave in Lead III must be a little greater.

RESULTS

The results are summed up separately for each of the aforementioned four groups of experimental subjects. As there were only insignificant differences attributable to sex and age, the results of the total analysis of all 100 cases will be given first.

THE P WAVE

In Leads I and II the P wave was positive in all 100 subjects except one, in whom it was diphasic ($-0.5 + 0.5$ mm.) in Lead II. In Lead III there occurred positive, diphasic, and negative P waves (Table I). In Leads I and II the P wave had most often the form of a gradual curve, and was pointed but seldom. It was only in 10 per cent of the cases, however, that the curve was entirely smooth; 90 per cent of the records showed from one to four small notches (or small waves). This notching was rarely so pronounced that the P wave might properly be designated as bifid; this was found only five times in Lead II.

In Lead I the average height of the P wave was 1.0 mm., and in Lead II it was 1.3 mm. In these two leads no P wave was lower than 0.5 mm., and none higher than 2.5 mm. The highest P wave in the individual subject was found seventy-nine times in Lead II, twenty-four times in Lead I, and once in Lead III. (That the total incidence of this property in the three leads in these and similar data is not 100 per cent is due to the fact that in cases in which, for instance, the P wave was of the same height in two leads and higher in these than in the third lead, we have recorded the P wave as being highest in both of the two leads concerned.)

The average duration of the P wave was 0.10 sec.; the shortest P wave lasted 0.070 sec., and the longest, 0.133 sec. In the individual subject the difference in the duration of the P wave in the different leads was 0.04 sec. at the most; eighteen subjects showed a difference greater than 0.02 sec., and, in fifty-seven cases, the difference was greater than 0.01 sec. The longest P wave was found thirty-two times in Lead I, fifty-one times in Lead II, and thirty-one times in Lead III. In the electrocardiographic literature, as a rule, 0.10 sec. is given as the upper limit for the normal duration of the P wave. In eighty-two of our 100 subjects the P wave lasted 0.10 sec. or more in at least one lead, and in six subjects, even 0.12 sec. or more. According to our observations, therefore, the P wave may be said to be abnormally wide only in cases in which its duration is 0.14 sec. or more in at least one lead.

TABLE I

THE P WAVE

	LEAD		
	I	II	III
Form (no. of subjects)			
Positive	100	99	67
Diphasic	0	1	24
Negative	0	0	9
Smooth	12	10	10
Notches	88	90	90
Bifid	0	5	0
Size (mm.)			
Minimum	0.6	0.5	0.9
Maximum	1.9	2.1	1.7
Av.	1.0	1.3	
P wave largest (no. of subjects)	24	79	1
Duration (sec.)			
Minimum	0.074	0.083	0.070
Maximum	0.133	0.132	0.128
Av.	0.100	0.103	0.099
0.10 sec. or more (no. of subjects)	58	69	46
0.12 sec. or more (no. of subjects)	4	6	4
P wave longest (no. of subjects)	32	51	31

THE P-Q SEGMENT AND THE P-Q INTERVAL

The P-Q segment signifies the section of the curve from the end of the P wave to the beginning of the QRS complex, whereas the P-Q interval (conduction time) signifies the time from the beginning of the P wave to the begining of the QRS complex. In about 95 per cent of the cases the course of the P-Q segment was horizontal; in the rest it was rising or going down (Table II). In Leads I and III the P-Q segment most often followed the isoelectric line. In Lead II the P-Q segment was below the isoelectric line in a little more than one-half of the cases; the P-Q segment took this course, also, fourteen times in Lead I and twenty-one times in Lead II. Further, in Lead III this segment was found above the isoelectric line in twelve cases. The maximal deviation from the isoelectric line in either direction was 0.5 mm.

The average duration of the P-Q interval was 0.163 sec.; the shortest duration was 0.107 sec., and the longest, 0.218 sec. In eight subjects the duration in one or more leads was 0.20 sec. or more; in two subjects the duration was over 0.21 sec., namely, 0.214 and 0.218 sec., respectively. In no subject was the duration of the P-Q interval simultaneously in all three leads less than 0.12 sec. In the present series the duration of the P-Q interval showed no relation to the pulse rate; but, of course, this does not exclude the possibility of such a relation in the individual person. Consequently, for "prolonged conduction time" we have to require that the duration of the P-Q interval be 0.22 sec. or more in at least one lead, and for "abnormally short conduction time" we have to demand a P-Q interval which lasts less than 0.12 sec. in all three leads. However, the conduction time may also be designated as prolonged in some cases in which the P-Q interval is less than 0.22 sec., namely, in those in which the conduction time is at least 0.02 sec. longer than it was in a previous electrocardiogram taken under the same conditions.

TABLE II

THE P-Q SEGMENT AND THE P-Q INTERVAL

	LEAD		
	I	II	III
Course of P-Q segment (no. of subjects)			
Horizontal	96	93	94
Rising	0	3	5
Falling	4	4	1
Isoelectric	86	46	67
Above isoelectric line	0	0	12
Below	14	54	21
Duration of P-Q interval (sec.)			
Minimum	0.112	0.121	0.107
Maximum	0.218	0.214	0.212
Av.	0.162	0.164	0.163
0.20 sec. or more (no. of subjects)	7	6	5
Less than 0.12 sec. (no. of subjects)	4	0	1
P-Q longest (no. of subjects)	35	47	40

The P-Q interval was longest in Lead I in thirty-five subjects, in Lead II in forty-seven, and in Lead III in forty. The greatest differences between the duration of this interval in the three leads in the individual subject were 0.05, 0.048, and 0.03 sec.; in nine subjects the difference was 0.02 sec. or more; in forty-nine subjects the difference was 0.01 sec. or more.

TABLE III

SIMULTANEOUS OCCURRENCE OF THE Q WAVE OR THE S WAVE IN THE DIFFERENT LEADS

WAVE	LEADS							
	I-II-III	I-II	I-III	II-III	I	II	III	NONE
Q	28	28	0	15	27	0	0	2
S	48	11	0	20	10	0	7	4

THE QRS COMPLEX

Form.—Most often the QRS complex was diphasic or triphasic; only in rare instances did it consist of a single wave, and, then, always of the R wave. Such a monophasic QRS complex occurred only two times in Lead I, seven times in Lead II, and six times in Lead III. The frequency of the Q and S waves is given in Table V, and Table III shows

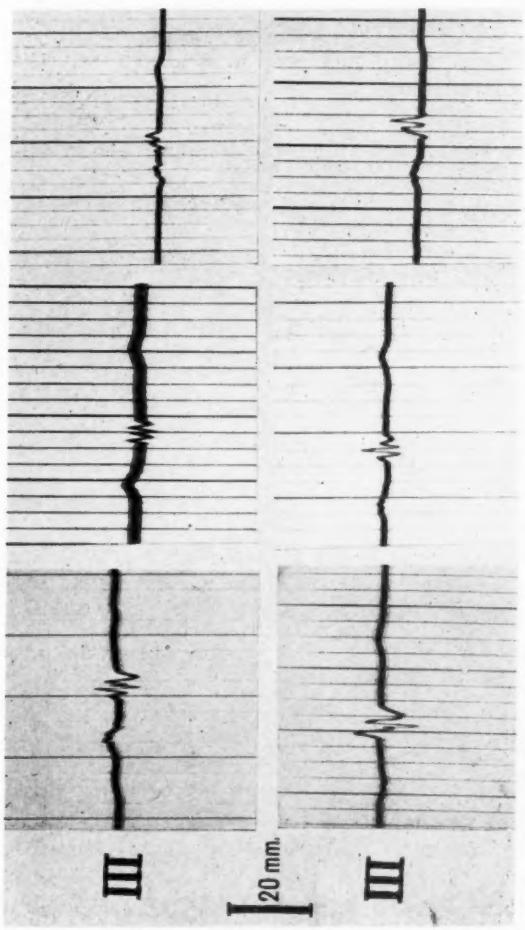

Fig. 1.—Irregular QRS complex in six normal subjects whose ages ranged from 30 to 50 years.

how often Q waves or S waves were found simultaneously in two or three leads. It will be noticed that neither the Q wave nor the S wave was ever found simultaneously in Leads I and III without being present in Lead II, and also that these waves never occurred in Lead II alone. This is in keeping with Einthoven's equation, namely, Lead II – Lead I = Lead III.

In some of the cases the QRS complex in Lead III was very irregular, with as many as three positive and negative waves, besides additional

nodules and notching. Some examples of such irregular complexes are shown in Fig. 1. In some cases the QRS complex was more than triphasic in Leads I and II, also, and the S wave was followed by a small positive wave. This wave has no designation in Einthoven's nomenclature, and hence it is sometimes designated as "innominate"; it occurred eleven times in Lead I, twelve times in Lead II, and eighteen times in Lead III. In Lead III this wave is known clinically as "the second positive R wave of Lead III," and diagnostic significance has been attached to its presence. For this reason it will be mentioned again in the last paragraph of this section.

Here mention is to be made also of the occurrence of nodules (punctate thickening) and notching of the waves. In order to avoid mistakes, we have to demand that the deformity must turn up again and again in a number of complexes. Still, the location of the deformities may vary a little; further, a deformity may turn up in some complexes as a nodule and in the following complexes appear as a slight notching. These variations are attributed to changes in the position of the heart caused by the respiratory movements. We have found it convenient to apply the designation *basal* to the nodules and notches located in that quarter of the waves that is nearest the isoelectric line, and deformities outside this part are designated as *apical*.

TABLE IV

OCCURRENCE OF NODULES AND NOTCHING ON THE R, Q, AND S WAVES

WAVE	DEFORMITIES	LEADS							
		I-II-III	I-II	I-III	II-III	I	II	III	NONE
R	Apical	20	1	8	14	13	5	21	18
R	Apical + basal	36	1	15	17	6	4	16	5
Q	Apical + basal	0	0	0	3	1	1	12	83
S	Apical + basal	5	4	2	18	7	4	19	41

From Table IV it is evident that nodules and notching are very common deformities of the R wave, but less frequent on the S wave, and particularly infrequent on the Q wave. The latter fact is due to the circumstance that the Q and S waves are absent in several derivations, and very small in others. Apical deformities on the R wave were found in twenty subjects simultaneously in all three leads, in twenty-three subjects simultaneously in at least two leads, and in thirty-nine subjects in only one lead; they were absent in all leads in eighteen subjects. Taking the apical and basal deformities together, they were present in thirty-six subjects simultaneously in all three leads, and in only five subjects was the R wave smooth in all three leads. In these five subjects, however, the Q wave or the S wave showed some notching or nodules, so that the QRS complex in no instance was free from these deformities simultaneously in all three leads.

After these observations, we are not able, like some clinicians, to attach any diagnostic significance to these deformities. It may be that notching of a certain degree is of some importance. On going through our records, we find, for instance, that in no case did the R wave in Leads I and II show apical notches in which the shortest limb measured more than 1 mm., or in which the shortest limb was longer than one-sixth of the height of the wave. But further investigation of this point is required.

Size and Duration.—The average size of the R wave was 7.7 mm. in Lead I, 10.2 mm. in Lead II, and 4.6 mm. in Lead III (Table V). In thirty subjects the R wave was highest in Lead I, in seventy subjects in Lead II, and in two subjects in Lead III. In fifteen subjects the R wave in Lead I was less than 5 mm. high; the same was the case in two subjects in Lead II, and in fifty-nine subjects in Lead III. On the other hand, in no instance did all three derivations from the same subject show an R wave less than 5 mm. in height; in other words, in this series no instance of "low voltage" occurred.

TABLE V

THE QRS COMPLEX

	LEAD		
	I	II	III
R wave (size in mm.)			
Minimum	1.8	4.1	0.7
Maximum	12.4	23.4	20.8
Av.	7.7	10.2	4.6
Less than 5 mm. (no. of subjects)	15	2	59
R wave largest (no. of subjects)	30	70	2
Q wave (size in mm.)			
Maximum	5.1	4.4	3.9
Av.*	0.7	0.9	1.1
Present (no. of subjects)	83	70	42
S wave (size in mm.)			
Maximum	5.4	5.8	7.6
Av.*	1.5	1.9	2.6
Present (no. of subjects)	72	79	74
Duration of QRS complex (sec.)			
Minimum	0.065	0.067	0.065
Maximum	0.108	0.118	0.121
Av.	0.084	0.087	0.088
0.08 sec. or more (no. of subjects)	62	69	70
0.10 sec. or more (no. of subjects)	4	12	12
QRS longest (no. of subjects)	26	42	52

*These averages are calculated per number of waves present.

Calculation of the dispersions on the size of the R wave showed that the dispersion was ±2.2 mm. in Lead I, ±3.1 mm. in Lead II, and ±3.4 mm. in Lead III. Taking the triple values of the dispersions as sufficiently safe limits for the normal variation in the size of the R wave, we may then characterize the R wave as abnormally high when it measures 20 mm. or more in Lead II, and 15 mm. in Leads I and III. In three of our subjects the height of the R wave fell outside these limits, namely,

in Case 83, in Leads II and III (R_2 = 23.4 mm., R_3 = 20.8 mm.), and in Cases 44 and 61 in Lead III (R_3, respectively, 15.4 and 16.7 mm.). The diagnostic significance of an abnormally high R wave is yet unsettled and has to be investigated on clinical material; among others, there is the question whether the R wave has to be abnormally high in all three leads in order to be of significance, or perhaps merely in one or two leads.

The Q wave was present twice as often in Lead I as in Lead III, whereas the occurrence of the S wave was about equally frequent in all three leads. From the average values it will be noticed that the Q wave in many cases was small.

In the three leads the average duration of the QRS complex varied between 0.084 and 0.088 sec. The difference in the duration of QRS in the different leads in the individual subjects was greater than 0.01 sec. in twenty-eight cases, and greater than 0.02 sec. in six cases; its maximum was 0.029 sec. The QRS complex was longest in Lead I in twenty-six subjects, in Lead II in forty-two, and in Lead III in fifty-two. The shortest measured duration was 0.065 sec., the longest, 0.121 sec. In eighty subjects the duration was 0.08 sec. or more in at least one lead, and in fourteen subjects it was 0.10 sec. or more. In the literature, 0.10 sec. is given as the upper limit for the normal duration of the QRS complex.[18] In order to make the diagnosis of intraventricular block,[18] the duration of the QRS complex has to exceed 0.12 sec.; a QRS complex lasting 0.10 to 0.12 sec. is characterized as "prolonged," with the addition that "such records are regarded by some as instances of incomplete bundle branch block." According to our observations, QRS complexes lasting from 0.10 to 0.12 sec. have to be looked upon as normal (for the age classes here examined), and the diagnosis of intraventricular block requires a QRS complex of more than 0.12 second's duration.

Left and Right Preponderance.—The question of preponderance is difficult to deal with because of the prevailing uncertainty as to which records show preponderance, and what these changes signify. In a subsequent work we hope we shall be able to return to these problems, and hence we shall here limit ourselves to a few brief remarks.

As is well known, for every point in the QRS complex it is possible to calculate and plot the angle for the electric axis and the value for the electrical potential when we know the potentials corresponding to the point in at least two derivations. Corresponding to the QRS complex, the end point of this vector follows a curve (vector diagram) of more or less irregular form. If this curve falls exclusively within the quadrant, with the angles from 0 to +90° (right lower quadrant), preponderance is out of the question. If, on the other hand, the greater part of the curve falls within the quadrant with the angles from 0 to –90° (right upper quadrant), there is preponderance of the left side of the heart; and, if the greater part of the curve falls within the quadrant with the

angles from +90° to +180° (left lower quadrant), there is right preponderance. One of the difficulties consists in giving simple rules to show which records correspond to the vector diagrams described. From theoretical studies, one of us (K. L.) has set up the following rules: *For right preponderance it is required that the S wave in Lead I exceed the R wave in the same derivation as to size and duration. For left preponderance it is required that the S wave in Lead III exceed the R wave in the same derivation as to size and duration, and also that it be greater than one-half of the R wave in Lead I.* After some preliminary studies[15] these rules appear to function satisfactorily; but they are not applicable to cases in which the QRS complex is markedly diphasic in all three derivations.

As we are not in possession of vector diagrams from our 100 subjects, we have analyzed the electrocardiograms according to the rules given above. We found left preponderance in five cases, namely, in two men (aged 35 and 41) and three women (aged 45, 46, and 47). In two of these subjects the body weight was above the normal average; on the other hand in neither case did the roentgenograms show any pronounced transverse position of the heart. In eighteen other subjects the S wave in Lead III was greater than the R wave, without being half as great as the R wave in Lead I. The greater part of the vector diagram corresponding to such a record will fall within the space between 0° and +30°, and hence the record may be designated as showing a tendency toward left preponderance. Of these eighteen subjects, twelve were men, and eight of these men were over 40 years old; all of the six women were over 40 years of age. Therefore, left preponderance and a tendency toward it were considerably more frequent in the age class of 40 to 50 years than in the age class of 30 to 40 years. In nine of these eighteen subjects the weight was above the normal average.

There was no instance of right preponderance, but in two cases the record was "right sided," i.e., the S wave in Lead I was approximately equal to the R wave. Both of these subjects were thin young men (aged 30 and 31), with wide chests.

Other Aspects of the QRS Complex.—No large Q_3[19] was observed in this series. On the other hand, in some of the cases the Q wave in Leads I and II exceeded the limits given by Kossmann, Shearer, and Texon[13] for the normal absolute and relative sizes of the Q wave, for Q_1 in two cases was greater than 2 mm., and in five cases greater than 15 per cent of the highest wave in all three derivations; and, in one case, Q_2 was greater than 20 per cent of the highest wave in all three derivations.

"M" or "W" complexes[4] were not encountered in Leads I and II, but they were seen in Lead III, where they are of no significance.

QRS complexes of the forms described by Proger and Minnich[20] (left preponderance with positive T_3 and $T_3 > T_1$ and/or $S_2 > \frac{1}{2} R_2$

and/or $T_1 < \frac{1}{7} R_1$) were encountered twice. Case 64 (a woman, aged 47) showed left preponderance, a positive T_3, and an S wave in Lead II that was greater than one-half of R_2; and Case 92 (a woman, aged 46) showed left preponderance, a positive T_3, and a T wave in Lead I that was smaller than $\frac{1}{7}$ of R_1.

As mentioned before, eighteen of our subjects showed, in Lead III, an additional positive wave after the R wave. In nine of these eighteen subjects the QRS complex in Lead III met the criteria set up by Katz and Slater[12] for "the second positive R wave of the QRS complex," for here the second positive wave occurred in records with left preponderance, or a tendency toward it; in six of the cases the second positive wave was greater than the first. Of these nine subjects, five were men (aged, respectively, 35, 35, 39, 46, and 47) and four, women (aged 41, 45, 46, and 47).

THE S-T SEGMENT

In Leads I and II the S-T segment proceeded most often obliquely upward (Table VI) because of the fact that in these derivations the T wave was always positive. In Lead III the segment was most often horizontal because of the diphasic, isoelectric, and negative T waves which occurred in this derivation. Saddle-shaped S-T segments[17] were seen in twenty-two subjects, in whom they occurred fourteen times in Lead I, thirteen times in Lead II, and four times in Lead III. In eighteen cases the saddle form was associated with the presence of an additional positive wave in the QRS complex; in the remaining thirteen cases the S wave was absent. On account of the frequent occurrence of a saddle-shaped S-T segment in a series like the present, we are not able to attach any great diagnostic importance to this change. Further investigation of this question is planned.

TABLE VI

THE S-T SEGMENT

	LEAD		
	I	II	III
Course			
Horizontal (no. of subjects)	12	12	63
Rising (no. of subjects)	74	75	17
Falling (no. of subjects)	0	0	16
Saddle-shaped (no. of subjects)	14	13	4
Isoelectric (no. of subjects)	40	36	47
Above isoelectric line (no. of subjects)	46	44	38
Maximal elevation (mm.)	1.3	0.9	1.2
Below isoelectric line (no. of subjects)	14	20	15
Maximal depression (mm.)	0.3	0.5	0.6

Deviations of the S-T segment from the isoelectric line, as mentioned, were always measured 0.05 sec. after the end of the QRS complex. This is expedient, for in this way we avoid designating as abnormally negative those S-T segments that fall more than 1 mm. under the isoelectric

line only just after their start from the QRS complex. The frequency of an isoelectric level and elevation and depression of the S-T segment in the various derivations is evident from Table VI—likewise, the maximal deviations of the S-T segment from the isoelectric line in either direction. In no instance did the S-T depression exceed 1 mm., and in no instance was the S-T elevation 1.5 mm. or more. Therefore, S-T segments showing such deviations will be designated as abnormal. It is to be added, however, that, in our estimation, no particular significance is to be attached to elevations of the S-T segment above 1.5 mm. if the form of the segment and the following T wave are normal.

In practice, the isoelectric line is often established as a horizontal line through the P-Q segment, especially in cases in which, because of a rapid heart beat, there is no horizontal segment between the end of the T wave and the beginning of the P wave. When there was an auricular T wave,[24] however, several subjects showed a depression of the P-Q interval. Then the question is how much the S-T segment has to deviate from the P-Q segment in order to be designated as abnormally negative. According to our observations, the requirement is that the S-T segment in Leads I and II, when there is no positive deflection of the P-Q segment (Table II), must be 1 mm. or more below the level of the P-Q segment; and in Lead III, in which the P-Q level may be as much as 0.5 mm. over the isoelectric line, the S-T segment must lie 1.5 mm. or more below the P-Q level. This means that we shall be unable to make a diagnosis of an abnormally negative S-T segment in several of those cases in which the S-T segment in Leads I and II was 1 to 1.5 mm. below the isoelectric line proper (in Lead III, 1 to 2 mm. below the isoelectric line), and in which the P-Q segment also was negative, but, as far as we can see, this cannot be helped.

THE T WAVE

In Leads I and II the T wave was positive in all 100 subjects; in Lead III it was positive in fifty-eight subjects, diphasic in twenty-five, isoelectric in six, and negative in eleven. The curve of the T wave was always quite smooth, i.e., free from the small notches that are so common in the P, R, and S waves.

In Lead I the average size of the T wave was 2.6 mm., and, in Lead II, 3.0 mm. In forty records the T wave was largest in Lead I, in sixty-two it was largest in Lead II, and in no instance was it largest in Lead III. In three of the subjects the height of the T wave in Lead I was less than 1 mm. In Lead II, on the other hand, the T wave was in no instance less than 1 mm. Therefore, in the present series there was no instance in which the T wave was less than 1 mm. in all three derivations. On calculation, the dispersion for the T wave in Lead I was found to be ± 0.96 mm.; and in Lead II it was ± 1.10 mm. If, as usual, we take the triple values for the dispersions as sufficiently safe limits for the normal

variations in the size of the T wave, we find that a T_1 of 6 mm. or more and a T_2 of 6.5 mm. (in practice, 7 mm., or more) may be designated as abnormally high. In our series these limits were exceeded only once, namely, in Case 80 (man, aged 39), whose T wave in Lead I was 6.5 mm. in height.

TABLE VII

THE T WAVE

	LEAD		
	I	II	III
Form			
Positive (no. of subjects)	100	100	58
Diphasic (no. of subjects)	0	0	25
Isoelectric (no. of subjects)	0	0	6
Negative (no. of subjects)	0	0	11
Size (mm.)			
Minimum	0.7	1.1	1.9
Maximum	6.5	5.8	4.3
Av.	2.6	3.0	
Less than 1 mm. (no. of subjects)	3	0	
T wave largest (no. of subjects)	40	62	0

In Lead III the largest negative T wave measured 1.9 mm. Of the two largest diphasic T waves, the negative phase measured respectively 1.2 and 1.1 mm., and the positive phase, 0.5 and 0.8 mm. In the other cases both phases measured less than 1 mm.

THE Q-T INTERVAL

Data on the duration of the Q-T interval are of significance only in connection with data on the average duration of the R-R interval, i.e., the pulse rate, because the duration of the Q-T interval is largely dependent upon the rate of the heartbeat. For this relation, formulas of different types have been devised; the best known are the one given by Bazett,[1] in 1920, namely, systole $= K \times \sqrt{\text{cycle}}$, in which Bazett found K to be 0.37 for men and 0.40 for women, and that given by Fridericia,[6] likewise in 1920, namely, $Q\text{-}T = 8.22\sqrt[3]{R\text{-}R}$. In Fridericia's equation the constants were ascertained from the examination of fifty normal persons of both sexes, whose ages ranged from 2 to 81 years; the limit of experimental error was found to be ± 0.045 sec.

The results of our study are recorded in Fig. 2, in which the duration of the R-R interval in seconds is plotted along the axis of abscissas, and the duration of the Q-T interval in seconds is plotted along the ordinate. The curve corresponding to Fridericia's equation is inserted in the figure. It will be noticed that the distribution of our data is uneven; in ninety-three of the cases the figures fell above Fridericia's curve, and below in only seven. The cause of this must be an error in the method. Since we were unable to find such an error in our study, we turned to

Fridericia's report, and noticed in particular that, even though Fridericia calls attention to the importance of an accurate timer, he fails to state whether his timer was adjusted, and how. On further investigation it was found that Fridericia's timer must have been running about

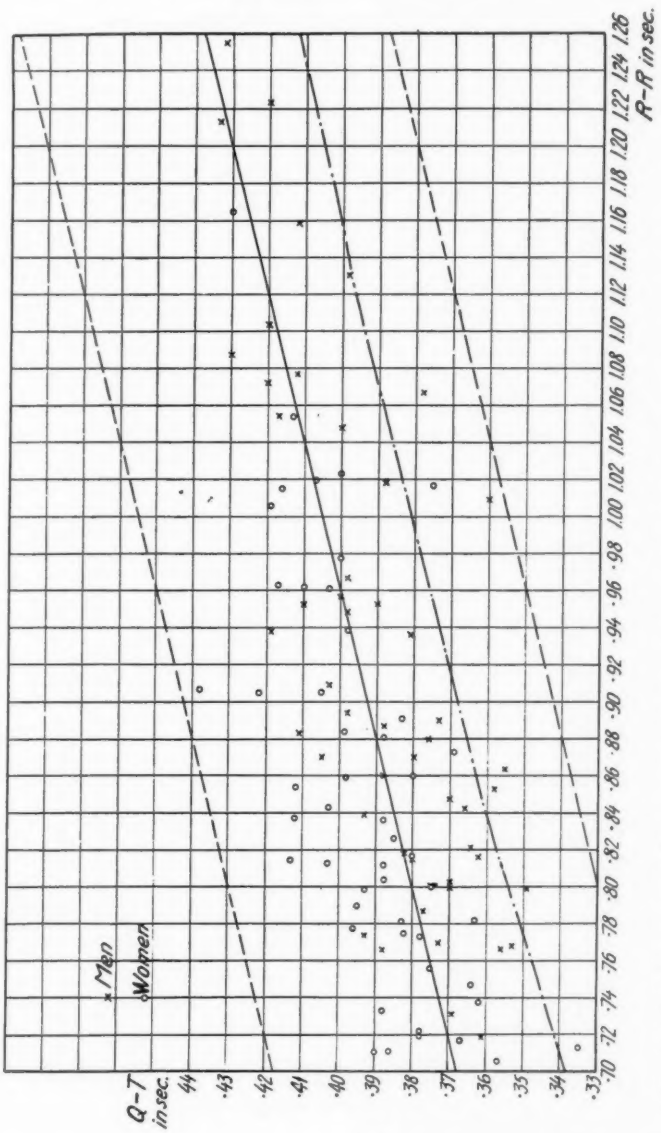

Fig. 2.—Graphic presentation of the relation between the R-R and Q-T interval. The duration of the R-R interval in seconds is plotted along the axis of abscissas, and the Q-T interval along the axis of ordinates.
–·–·–·–, Line corresponding to Fridericia's equation.
———, Line corresponding to the authors' equation.
– – – –, The limits of error for the line corresponding to the authors' equation.

10 per cent too slow in order to be able to cause all the difference between his results and ours. And, in our opinion, an error of 10 per cent in the measuring of such short periods as those concerned here is not large enough to attract attention without regular and systematic adjustment.

Instead of correcting Fridericia's equation according to our results, we have done something else. A glance at Fig. 2 shows that the curvature of Fridericia's curve in the field of frequency with which we are concerned (48-85) is so slight that the curve may readily be replaced by a straight line. The equation for this line must be the formula $Y = a \cdot x + b$. We have ascertained the constants by graphic plotting, and arrived at the following result:

$$Q\text{-}T = 0.125 \times R\text{-}R + 0.28 \text{ sec.}$$

In this equation Q-T and R-R are given in seconds. Although this equation was obtained graphically, it is fully satisfactory for our data, as is evident from the fact that, in our 100 cases, the standard deviation from the line corresponding to this equation was –0.00052 sec., i.e., very insignificant.

The mean error (m) of the individual deviation (A) may be calculated from the formula $m = \pm\sqrt{\frac{\Sigma\ A^2}{n-2}}$ in which n is the number of observations, and is found to be ±0.0164 sec. Therefore, the actual limit of error is ± 0.0492, or, practically, ±0.05 sec. Both the lines corresponding to the obtained equation and those corresponding to the limits of error are plotted in Fig. 2, and it will be noticed that, in all our 100 cases, the figures fell within the field marked off in this way.

The obtained equation may be written as follows:

$$Q\text{-}T = \tfrac{1}{8}\ R\text{-}R + 0.28 \pm 0.05 \text{ sec.}$$

In this form the equation is so easy to remember and employ that the examiner at the bedside may readily decide whether or not the Q-T interval is of normal duration, without the use of tables or other adjuvants.

It is worth while, we believe, to look into the question whether there is any difference in the duration of the Q-T interval in the two sexes. The studies reported by Bazett were suggestive of such a difference, and further analysis of Fig. 2 shows that in a majority of our female subjects the Q-T interval had a positive deviation from the mean line, whereas the Q-T interval in a majority of the male subjects showed a negative deviation. The average deviation for the fifty women was +0.0088 sec., and for the fifty men it was –0.0098 sec., which suggests that the Q-T interval is of longer duration in women than in men, but the total difference between the women and men was 0.0176 sec., and this is so small in proportion to the mean error of the deviations in the two groups that it is not significant statistically. It will require a considerably greater number of observations to settle the question of a possible sex difference.*

*Dr. Jorgen Frost has called our attention to the fact that Adams and Sebastiani previously have derived formulas of the same type as ours for the relation between the Q-T and R-R intervals. Adams' formula (J. Clin. Investigation 15: 335, 1936) is Q-T = 0.1464 R-R + 0.2572 sec., and gives values for Q-T which, with rates from 40 to 90, are only 4.3 to 1 per cent below the values calculated from our formula. The formula of Sebastiani (Arch. d. mal. du coeur 31: 973, 1938) is Q-T = 1/10 R-R + 22.2 sec., and gives an all-too-short duration of the Q-T interval.

THE U WAVE

The U wave always had the form of a low, smooth, upward, convex—i.e., positive—curve. No negative U wave was observed. Our subjects' heart rates were such that the U wave was always free of the T as well as the P wave. In Lead I the U wave was visible in fifty-seven subjects, in Lead II in eighty-three, and in Lead III in forty. In fifteen subjects the U wave could not be seen in any of the three derivations.

ARRHYTHMIAS

Distinct respiratory arrhythmia, i.e., variations in the R-R interval of 0.10 sec. or more, occurred in twenty-four subjects, thirteen of whom were women, and eleven, men.

One man, aged 45, showed a single ventricular extrasystole. None of the subjects had any sensation of extrasystoles.

Other arrhythmias were not encountered.

SEX AND AGE DIFFERENCES

All the features of the electrocardiogram mentioned in the preceding sections were examined with a view to ascertaining whether there were sex and age differences. In all positive and doubtful cases we have ascertained whether the difference between the two averages was greater or smaller than three times the value of the mean error of the difference (m_D). As is well known, the formula for m_D is $m_D = \sqrt{m^2_A + m^2_B}$, in which m_A and m_B are the mean error of the two averages. The results are given in Table VIII, in which the statistically significant differences are shown in italics.

TABLE VIII

SEX AND AGE DIFFERENCES

	MEN	WOMEN	30-40 YEARS	40-50 YEARS
Av. height of waves (mm.) (Lead II)				
P wave	1.3	1.3	1.3	1.3
R wave	10.8	9.6	10.5	9.9
T wave	3.4	2.7	3.0	3.1
Av. duration (sec.) (Lead II)				
P wave	0.106	0.101	0.102	0.105
P-Q interval	0.168	0.160	0.163	0.165
QRS complex	0.092	0.083	0.088	0.086
Other components (no. of subjects)				
P-Q positive in Lead III	*1*	*11*	8	4
S-T positive in Lead I	*34*	*12*	26	20
S-T positive in Lead II	*30*	*14*	23	21
Saddle-shaped S-T	10	12	*5*	*17*
Left preponderance and "lefty"	14	9	*5*	*18*
"Second positive R_{III}"	5	4	3	6
Respiratory arrhythmia	11	13	16	8

As is evident from Table VIII, the waves on an average are higher in men than in women, and the average durations of the P wave, P-Q

interval, and QRS complex are a little longer in men than in women. As mentioned before, the opposite applies to the Q-T interval, which on an average is a little longer in women than in men. The difference is too small, however, to be statistically significant. To settle the question of a possible sex difference, which might perhaps be due solely to a difference in the size of the bodies, a considerably larger series of cases would be required. In the two age classes here considered (persons between 30 and 40 years, and between 40 and 50 years), the mentioned components showed only insignificant differences.

In the present series the only definite sex difference was in the form of the P-Q and S-T segments. In Lead III the P-Q level was more often above the isoelectric line in women than in men, and in Leads I and II the S-T level was more often above the isoelectric line in men than in women. These features are of no significance in clinical electrocardiography.

The two age groups showed a statistically significant difference in the frequency of occurrence of a saddle-shaped S-T segment and left preponderance; both changes were more frequent in the older subjects. The same applies to the occurrence of the second R wave in Lead III, whereas respiratory arrhythmia was more common in the younger subjects; but these two differences were not statistically important.

CORRELATIONS

The correlations between the components of the electrocardiogram were studied by means of graphic presentations, and, in doubtful cases, by calculation of the coefficient of correlation (r). Between the duration of the R-R interval (pulse rate) and the other components in Lead II the correlations given in Table IX were found to exist.

TABLE IX

R-R interval and height of the P wave	No correlation (diagram)
R-R interval and duration of the P wave	No correlation (diagram)
R-R interval and P-Q interval	$r = +0.23 \pm 0.095$
R-R interval and height of the R wave	$r = -0.06 \pm 0.10$
R-R interval and duration of QRS	$r = +0.31 \pm 0.090$
R-R interval and height of the T wave	$r = +0.42 \pm 0.082$
R-R interval and Q-T interval	$r = +0.69 \pm 0.052$

As was to be expected, this analysis shows that there is a definite positive correlation between the R-R interval and the Q-T interval, and, further, that there are statistically significant, although slight, positive correlations between the R-R interval and the duration of QRS, and between the R-R interval and the height of the T wave. These observations mean that protracted QRS complexes and high T waves are more frequent in persons who at rest have a slow pulse rate than in persons who at rest have a more rapid pulse rate. Further, it will be noticed that r, on the whole, is increasing in the sequence given

above. This means that those components of the electrocardiogram that are caused by contraction of the myocardium are more dependant upon the pulse rate, in contrast to, or in a higher degree than are, the components caused by propagation of the impulse.

For other pairs of components in Lead II the correlations given in Table X were found.

TABLE X

Height of P and duration of P	No correlation (diagram)
Height of R and height of P	No correlation (diagram)
Height of R and duration of QRS	No correlation (diagram)
Height of R and height of T	$r = +0.30 \pm 0.094$
Height of T and duration of Q-T	$r = +0.24 \pm 0.094$

Thus, there was a very slight positive correlation between high R waves and high T waves, but no definite correlation, or no correlation at all, in the other cases.

In discussing the slight sex differences that are evident in Table VIII, we suggested that they might possibly be due merely to a difference between the size of the male and female body. Taking the surface area as a measure of body size, we found that the fifty women had an average surface of 1.70 sq.m., and the fifty men an average surface of 1.86 sq.m. We then studied the correlation between body surface and the two components of the electrocardiogram that show the greatest sex difference (Table XI).

TABLE XI

Body surface and height of R_2	$r = +0.03 \pm 0.10$
Body surface and duration of QRS_2	$r = +0.31 \pm 0.09$

The statistically significant, positive, but slight, correlation between the body surface and the duration of the QRS complex lends support to the assumption set forth, at any rate as far as this component is concerned.

SUMMARY

The present work is an analysis of the extremity derivations from 100 normal persons (fifty women and fifty men) whose ages ranged from 30 to 50 years. After a thorough account of the experimental subjects, the electrocardiographic apparatus, and the technique employed in measuring of the electrocardiograms, the results are reported. Essentially, these results are evident from the tabulations.

REFERENCES

1. Bazett, H. C.: Heart **7**: 353, 1920.
2. Benedetti, P. and Sabena, V.: Arch. di pat. e clin. med. **17**: 491, 1938 (cited after Zentralbl. f. d. ges. inn. Med. **97**: 128, 1938).
3. Chamberlain, E. N., and Hay, J. D.: Brit. Heart J. **1**: 105, 1939.
4. Edeiken, J., and Wolferth, C. C.: Am. J. M. Sc. **188**: 842, 1934.

5. Einthoven, W.: Pflüger's Arch. f. d. ges. Physiol. **122**: 517, 1908.
6. Fridericia, L. S.: Acta med. Scandinav. **53**: 469, 1920.
7. Groedel, F. M.: Das Extremitäten-, Thorax- und Partial-Elektrokardiogramm des Menschen, Dresden, 1934, Th. Steinkopff.
8. Gross, K.: Ztschr. f. Kreislaufforsch. **26**: 545, 1934.
9. Hadorn, W.: Ibid. **27**: 545, 1935.
10. Jenner, Hoskin, and Jonescu, P.: Brit. Heart J. **2**: 33, 1940.
11. Jensen, J., Smith, M., and Cardwright, E. D.: Am. Heart J. **7**: 718, 1932.
12. Katz, M. S., and Slater, S. R.: Arch. Int. Med. **55**: 86, 1935.
13. Kossmann, C. E., Shearer, M., and Texon, M.: Am. Heart J. **11**: 346, 1936.
14. Larsen, Kaj: Om Forandringer i Elektrocardiogrammet hos Sunde og Syge under experimentel Iltmangel. Dissertation. Copenhagen, 1938, Ejnar Munksgaard.
15. Larsen, Kaj, and Frost, J.: (To be published.)
16. Lewis, Th., and Gilder, M. D.: Phil. Tr. Roy. Soc. London **202B**: 351, 1912.
17. Van Nieuwenhuizen, C. L. C., Hartog, H. A. Ph., and Matthijssen, E.: Acta med. Scandinav. **98**: 468, 1939.
18. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, 1939, New York Heart Association.
19. Pardee, H. E. B.: Arch. Int. Med. **46**: 470, 1930 (II).
20. Proger, S. H., and Minnich, W. R.: Am. J. M. Sc. **189**: 674, 1935.
21. Schulz, W.: Ztschr. f. klin. Med. **135**: 137, 1938.
22. Shipley, R. A., and Hallaran, W. R.: Am. Heart J. **11**: 325, 1936.
23. Skúlason, Th., and Larsen, Kaj: Am. Heart J. **22**: 645, 1941.
24. Sprague, H. B., and White, P. D.: J. Clin. Investigation **1**: 389, 1925.
25. Warnecke, B.: Ztschr. f. Kreislaufforsch. **31**: 391, 1939.

THE NORMAL ELECTROCARDIOGRAM

II. Analysis of Precordial Derivations *d* and *s* from 100 Normal Persons Whose Ages Ranged From 30 to 50 Years

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IN RECENT years, derivations from the precordium have been employed extensively in clinical electrocardiography. Hence an analysis of these derivations in normal persons is highly desirable. This is a big task, however, for many different precordial derivations have been in use in various clinics. But we believe that it would not be rational to prefer certain derivations from theoretical considerations alone, and, inasmuch as there is not yet sufficient clinical experience to make a choice, it will be necessary for the time being to work on a broad front.

Most of the studies reported so far on precordial derivations in normal persons deal with Lead IV, as used first by Wolferth and Wood.[29] This is a ventrodorsal derivation, with the exploring electrode placed either at the left sternal margin (Wolferth and Wood,[29] Katz and Kissin,[10] Goldbloom,[3] Master,[17] Holzmann[8]), or over the apex (Hoffman and Delong,[7] Lieberson and Liberson[16]), and with the indifferent electrode placed on the back. Other investigators have used the now prevailing precordial derivations in which the indifferent electrode is applied either to the left leg (Wood, Bellet, McMillan, and Wolferth,[30] Shipley and Hallaran,[23] Robinson, Contratto, and Levine[21]), or to the right arm (Groedel,[4] Roth,[22] Wood and Selzer,[32] Hoskin and Jonescu[9]) or, as suggested by Wilson, Johnston, Macleod, and Barker,[27] is paired with a central terminal connected through equal resistances of 5,000 or more ohms to electrodes on the right arm, left arm, and left leg (Kossmann and Johnston[12]). Finally, some investigators have reported comparative studies with several of these leads (Shipley and Hallaran,[23] Holzmann,[8] Sorsky and Wood,[24] Groedel[5]). In the following, details from these studies will be mentioned occasionally.

In this paper an analysis will be made of two precordial derivations, called *d* and *s*, from 100 normal persons whose ages ranged from 30 to 50 years. In Lead *d* the exploring electrode is placed so that its center is at the apex of the angle between the left costal margin and the xiphoid process; in Lead *s*, the exploring electrode is placed so that its center is 4 cm. to the left of, and at the level of, the apex beat. In both derivations the indifferent electrode is applied to the right arm. Our Lead *d*

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is identical with the Lead *d* used by Groedel,[4] whereas our Lead *s* differs from that of Groedel, for Groedel always takes his derivation from the left anterior axillary line at the level of the xiphoid process, regardless of the location of the apex beat. The reasons why we have chosen these derivations have been given in previous papers (Larsen,[13] Larsen and Warburg[15]); at the conclusion of the present paper we shall repeat and elaborate our arguments. Here it will suffice merely to point out how our Leads *d* and *s* are related to the precordial derivations recommended by the American Heart Association.[25, 26]

If only one precordial derivation is wanted, the American Heart Association recommends that it be taken from "the extreme outer border of the apex beat." With the indifferent electrode applied to the right arm, this lead, designated as Lead IVR, differs from Lead *s* in this respect, namely, that the site of derivation from the chest is located 3 to 4 cm. medial to that of Lead *s*. For taking several precordial electrocardiograms, six different sites of derivation on the chest are recommended, using one of the aforementioned indifferent electrodes, as the examiner may wish. One of the derivations obtained in this way is called Lead CR_2, and it differs from Lead *d* merely in this respect, namely, that its site of derivation on the chest is located 3 to 6 cm. more cephalad than that of Lead *d;* for CR_2 is a derivation from the left sternal margin in the fourth intercostal space, and the right arm. Another of the recommended derivations, CR_5, is identical with Groedel's Lead *s*, but differs from our Lead *s* in this, that the site of derivation does not vary with the location of the apex beat.

EXPERIMENTAL SUBJECTS AND TECHNIQUE

The present studies were carried out on 100 normal subjects whose ages ranged from 30 to 50 years; there were twenty-five women and twenty-five men aged from 30 to 40, and twenty-five women and twenty-five men aged from 40 to 50. In a previous paper (Larsen and Skúlason[14]) we analyzed the extremity derivations from these subjects, and gave an account of the subjects and a detailed description of the electrocardiographic apparatus and the technique employed in measuring the records.

Leads *d* and *s* were recorded simultaneously; the left arm wire was connected to the *d* electrode, and the left leg wire to the *s* electrode; the right arm electrode served as the indifferent one. The sites of derivation were determined by palpation. In cases in which the apex beat was not palpable, and when the location of the left border of the heart could not be ascertained by percussion, the *s* electrode was placed in the fifth intercostal space, with its center 4 cm. lateral to the midclavicular line. The electrodes were flat discs of rustproof steel, with a diameter of 3 cm.; two holes were punched in the electrodes, through which an elastic band kept them fixed to the chest. Pieces of felt, of the same size as the electrodes, were moistened with warm salt solution and placed under the electrodes.

As in the analysis of the extremity derivations, the present results are analyzed separately for each of the four groups of subjects, but an account is given first of the entire group, and then the records are examined with a view to sex and age

differences. For the sake of comparison with the limb leads, some of the results obtained with Lead II are included in the tabulation of the present observations.

RESULTS

The P Wave.—In ninety-nine of the 100 subjects the P wave was positive in Lead *d* and Lead *s*. In one subject the P wave was diphasic in both leads, measuring, respectively, +1.6, –0.8 mm. and +1.6, –0.6 mm. This was not the subject who showed a diphasic P wave in Lead II. Most often the P wave had the form of a rounded arch; pointed forms were infrequent. Minor notching was very common (Table I), whereas a bifid P wave occurred only twice in Lead *d* and once in Lead *s*. The average height of the P wave was 1.5 mm. in both derivations. The smallest P wave was a little less than 1 mm. in height, and the largest was hardly 2.5 mm. in height. In both derivations the average duration of the P wave was 0.10 sec. In eight subjects the duration of the P wave in one or both precordial leads was 0.12 sec. or more, and in 2 subjects it was 0.13 sec. or more.

TABLE I

THE P WAVE

	LEAD		
	d	*s*	II
Form (no. of subjects)			
Positive	99	99	99
Diphasic	1	1	1
Negative	0	0	0
Smooth	7	6	10
Notches	93	94	90
Bifid	2	1	5
Size (mm.)			
Minimum	0.8	0.8	0.6
Maximum	2.3	2.3	2.1
Av.	1.5	1.5	1.3
Duration (sec.)			
Minimum	0.078	0.078	0.083
Maximum	0.130	0.133	0.132
Av.	0.102	0.104	0.103
0.10 sec. or more (no. of subjects)	55	66	69
0.12 sec. or more (no. of subjects)	5	5	6

As is evident from Table I, the resemblance between the P wave in Leads *d* and *s* and that in Lead II (and Lead I) is so great that the same criteria for normality of the P wave may be applied to all four leads. These criteria are as follows: The P wave is positive, or, exceptionally, diphasic, with a small negative phase; its size varies from 0.5 to 2.4 mm., and its duration from 0.07 to 0.135 sec. In order to be "high," therefore, the P wave has to measure at least 2.5 mm.; and a "wide" P wave has to have a duration of at least 0.14 sec.

THE P-Q SEGMENT AND THE P-Q INTERVAL

The course of the P-Q segment was most often horizontal; less frequently it rose or fell (Table II). In eighty-one subjects the P-Q level

in Lead *d* was below the isoelectric line for a longer or shorter distance, with a maximal depression of 0.7 mm. In Lead *s* fifty-two subjects had a maximal P-Q segment depression of 0.8 mm. In one subject the P-Q segment was 0.1 mm. above the isoelectric line in Lead *d;* in another subject the same thing occurred in Lead *s*. In the rest of the records the P-Q segment kept at the level of the isoelectric line.

TABLE II

THE P-Q SEGMENT AND THE P-Q INTERVAL

	LEAD		
	d	*s*	II
Course of P-Q segment (no. of subjects)			
Horizontal	78	78	93
Rising	17	17	3
Falling	5	5	4
Isoelectric	18	47	46
Above isoelectric line	1	1	0
Below isoelectric line	81	52	54
Duration of P-Q interval (sec.)			
Minimum	0.120	0.119	0.121
Maximum	0.218	0.213	0.214
Av.	0.163	0.163	0.164
0.20 sec. or more (no. of subjects)	4	5	6
Less than 0.12 sec. (no. of subjects)	0	1	0

The duration of the P-Q interval was the same as in the extremity derivations (Table II). In five subjects the duration of the P-Q interval in Lead *d* and/or Lead *s* was 0.20 sec. or more. Therefore, even when the limb leads are supplemented with one or more precordial leads, the conduction time may be designated as abnormally short only if the duration of the P-Q interval in all derivations is less than 0.12 sec., whereas "prolonged conduction time" requires only that the duration of the P-Q interval be 0.22 sec. or more in at least one of the leads employed.

THE QRS COMPLEX

Form.—In Lead *d* the QRS complex was most often diphasic, consisting of an R wave and an S wave. A monophasic complex did not occur at all, whereas a triphasic complex was recorded eleven times; a Q wave was present in eleven subjects. This Q wave, which will be mentioned later, was always small; it measured only 0.3 mm. in eight subjects, and in three it measured, respectively, 0.6, 0.9 and 1.2 mm. A "second R wave," i.e., a positive wave after the S wave, was not found in any record. Table III gives additional information about the form of the QRS complex. It will be noticed that in exactly one-half of the subjects the R wave was greater than the S wave. In eighteen subjects the R wave was more than twice as large as the S wave, so that in these cases the R wave dominated the complex. Correspondingly, the S wave was the dominant wave in eleven subjects. This leaves seventy-one subjects whose R waves and S waves were about of equal size.

In Lead *s* the QRS complex was triphasic in sixty-nine subjects, consisting of a large R wave and smaller Q and S waves. A diphasic complex was found in twenty-nine subjects; it consisted of an R wave and an S wave in twenty-six, and of a Q wave and an R wave in three. A monophasic complex consisting of the R wave alone was found in two subjects. In this numerical survey the presence of a "second R wave" is left out of consideration; such a wave was present in ten subjects, and was always very small (up to 2 mm., see Fig. 1*A*). The relative size of the R wave and the S wave in the various subjects is evident from Table III. In all subjects but one the R wave was greater than the S wave, and in eighty-nine subjects the R wave was more than twice as great as the S wave, so that it was the dominating wave in the complex. In eleven subjects the R wave and the S wave were about of equal size, and in one of these the S wave was a little larger than the R wave.

TABLE III

PROPORTION OF SIZE BETWEEN THE R WAVE AND THE S WAVE

LEAD	R>2 S	2 S>R>S	2 R>S>R	S>2 R
d	18	32	39	11
s	89	10	1	0

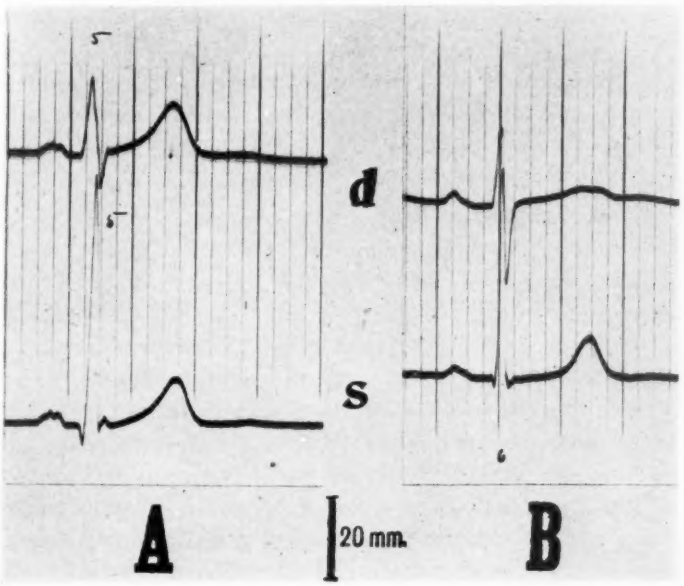

Fig. 1.—Precordial derivations *d* and *s* from two normal subjects, aged from 30 to 50 years. In *A* there is a small "second R wave" in Lead *s*; in *B* there is a plateau formation of the T wave in Lead *d*.

The occurrence of slurring and notching is recorded after the same principles as were employed by us[14] previously in dealing with the extremity derivations. The result is given in Table IV. Slurring and

notching were more frequent in Lead *d* than in Lead *s*, especially of the R wave, but also of the S wave. Taking apical and basal deformities together, these phenomena were present in seventy-five subjects in the R wave in Lead *d*, and in only twenty-seven subjects in the R wave in Lead *s;* for the S wave the corresponding figures were 52 and 38. Simultaneous apical deformity of the R wave in both leads was found in thirteen subjects; in only seventeen subjects was the R wave smooth in both leads, and there was deformity of the S wave in eight of these seventeen subjects. There was no deformity of the little Q wave; although the descending limb of this wave was often thickened, it was always smooth. The notches were always small; as in the extremity derivations, the shortest limb of the notching never measured more than 1 mm. In view of the very great frequency of the nodules and notches in a series like this, we have to conclude that these deformities are of no practical significance, either in the extremity derivations or in the precordial, no matter whether they are present only in one lead or simultaneously in more, or occasionally in all the leads, and regardless of whether they are apical or basal.

TABLE IV

OCCURRENCE OF NODULES AND NOTCHING ON THE R, Q, AND S WAVES

WAVE	DEFORMITIES	LEAD			
		d and *s*	*d*	*s*	NONE
R	Apical	13	59	4	24
R	Apical + basal	19	56	8	17
Q	Apical + basal	0	0	0	100
S	Apical + basal	29	23	9	39

Size and Duration.—In Lead *d* the average size of the R wave was the same as that of the S wave, namely, 7.7 mm. (Table V). The smallest R wave measured 2.1 mm. in height, the highest R wave, 19.7 mm.; the S wave varied between 0.6 and 19.4 mm. The frequency and size of the Q wave in Lead *d* has been mentioned already. In Lead *s* the average size of the R wave was 23.9 mm.; the smallest R wave was 10.8 mm. in height, the highest, 45.7 mm. The S wave was present in ninety-five subjects; it varied between 0 and 22.6 mm., with an average of 5.5 mm. The Q wave was present in seventy-two subjects; it varied between 0 and 6.1 mm., with an average size of 1.2 mm. In order to get a more definite and reliable idea about the normal variations, we have calculated the dispersions (s) for some of the waves, as shown in Table VI, in which m is the average.

It is evident from the figures in Table VI that the calculated minimum limits can be of no real significance—something that is often encountered in biologic studies. In setting the limits for the normal variations (see the last column), therefore, we employed the experimental results for the minimum limits, and took the calculated values for the maximum

limits. In our series the limits established in this way were exceeded in only three subjects: in Case 83 (man, aged 37), the R wave in Lead *d* measured 19.7 mm.; in Case 45 (man, aged 40), R_s measured 45.7 mm.; and in Case 44 (man, aged 30), S_s measured 22.6 mm. The significance of small R waves will be mentioned later. The significance of large R and S waves is still unsettled.

TABLE V

THE QRS COMPLEX

	LEAD		
	d	*s*	II
R wave (size in mm.)			
Minimum	2.1	10.8	4.1
Maximum	19.7	45.7	23.4
Av.	7.7	23.9	10.2
Q wave (size in mm.)			
Maximum	1.2	6.1	4.4
Av.*	0.4	1.2	0.9
Present (no. of subjects)	11	72	70
S wave (size in mm.)			
Minimum	0.6	0.0	0.0
Maximum	19.4	22.6	5.8
Av.*	7.7	5.5	1.9
Present (no. of subjects)	100	95	79
Duration of QRS complex (sec.)			
Minimum	0.070	0.073	0.067
Maximum	0.120	0.116	0.118
Av.	0.091	0.089	0.087
0.08 sec. or more (no. of subjects)	83	78	69
0.10 sec. or more (no. of subjects)	20	11	12

*These averages are calculated per number of waves present.

TABLE VI

	M (MM.)	S (MM.)	CALCULATED		MEASURED		NORMAL VARIATIONS (MM.)
			MINIMUM M−3S (MM.)	MAXIMUM M+3S (MM.)	MINIMUM (MM.)	MAXIMUM (MM.)	
R_d	7.7	3.1	−1.6	17.0	2.1	19.7	2 – 17
S_d	−7.7	4.1	+4.5	−19.9	−0.6	−19.4	−0.5 – −20
R_s	23.9	6.5	4.6	43.3	10.8	45.7	10 – 45
S_s	−5.5	3.7	+5.7	−16.7	0.0	−22.6	0 – −17

Several investigators (Holzmann[8] and Wood and Selzer[32]) state that in leads from the apex region the R wave is high in patients with left preponderance in the extremity leads, and, conversely, in patients with right preponderance the R wave is particularly high in the sternal derivations. Groedel[4] has taken particular interest in the proportion between the "intrinsic deflection" in Lead *d* and the corresponding deflection in Lead *s*, and, among other things, reasoning from the studies reported by Koch and Galli,[11] he believes that this proportion gives reliable information about the weight proportion between the right ventricle and the left. The size of the "intrinsic deflection" may be measured by the sum of the R and T waves. In normal persons Groedel finds that the

coefficient $(R + S)_d : (R + S)_s$ varies between 1.0 and 1.5; in patients with right preponderance the coefficient is greater than 1.5, and, in patients with left preponderance, smaller than 1.0. In view of these statements we have examined both the proportion $(R + S)_d : (R + S)_s$ and the proportion $R_s : R_d$.

The value for the "intrinsic deflection" in Lead *d* varied between 6.7 and 31.1 mm. (averaging 15.7 mm.), and, in Lead *s*, between 15.6 and 62.1 mm. (averaging 29.4 mm.). The proportion $(R + S)_s : (R + S)_d$ varied between 1.08 and 3.73, averaging 2.04. Thus the "intrinsic deflection" was always greater in Lead *s* than in Lead *d*, but in no instance was it four times as large in Lead *s* as in Lead *d*. In five subjects with left preponderance in the extremity leads the average value for the above proportion was 1.78, and in eighteen subjects with a tendency toward left preponderance it was 2.07, but in these subjects there was no evidence to the effect that the preponderance of the left side was due to hypertrophy of the left ventricle. The minimum values for the sum of the R and S waves in the two derivations (6.7 mm. in Lead *d* and 15.6 mm. in Lead *s*) may be taken for guidance in deciding whether or not there is any "low voltage" in the precordial leads.

The proportion $R_s : R_d$ varied between 1.62 and 14.50, averaging 3.61. In only three subjects was the coefficient greater than 6.50, i.e., respectively, 8.40, 13.0, and 14.50, and in one of these there was a tendency toward left preponderance in the extremity derivations. In the five subjects with left preponderance in the extremity derivations the average of the above-mentioned proportion was 3.26, and in the eighteen subjects with a left preponderance tendency it was 3.77.

The average duration of the QRS complex was 0.091 sec. in Lead *d*, and 0.089 sec. in Lead *s*, i.e., a little bit longer in the precordial leads than in the limb leads. Including the derivations in which the QRS complex was of the longest duration, it is found that this was the case in five subjects in Lead I, in thirteen subjects in Lead II, in twenty-seven in Lead III, in forty-five in Lead *d*, and in thirty-six in Lead *s* (the number of subjects counted in this way exceeds 100 because the QRS complex in some cases was equally long in two or three leads and longer than in the other derivations). In several cases the duration of the QRS complex was 0.10 sec. or more. Considering all five derivations together, it was found that the duration in twenty-three subjects was between 0.10 and 0.12 sec. in at least one derivation. We take such a duration of the QRS complex as normal for the age groups here considered, except in cases in which a previous electrocardiogram had shown a shorter duration.

Other Aspects of the QRS Complex.—All investigators agree in looking upon *complete absence of the R wave* in the precordial leads as pathologic. This phenomenon was observed first by Wilson, Macleod,

Barker, Johnston, and Klostermeyer[28] in cases of anterior cardiac infarction, but later it was encountered with many other lesions, especially those which produce bundle branch block or marked preponderance of the left side (e.g., Holzmann,[8] Master, Dack, Kalter, and Jaffe[18]). In other patients with the same lesions the records have shown an *abnormally small R wave*, and the limit for such a wave is set by most investigators at 2 mm. None of these changes occurred in our series. According to our observations, the R wave may be designated as abnormally small if it is less than 2 mm. in Lead *d*, and less than 10 mm. in Lead *s*.

Holzmann[8] looks upon complete absence of the R wave in the precordial leads as a result of *abnormal increase in the S wave at the expense of the R wave*, and he states that the proportion R:S in the derivation employed by him—from the left sternal margin to the back—in normal subjects is never as small as 1:10. In Lead *d* the proportion R:S varied between 10.3 and 0.21, and this means that the S wave in Lead *d* in our 100 subjects was never five or more times greater than the R wave. In Lead *s*, as mentioned before, only one subject had an S wave which was greater than the R wave.

"M" and "W" complexes, which have been observed by Wood and Wolferth,[31] Mortensen,[19] and others, in cardiac infarction, and which are present also in cases of bundle branch block, did not occur in any of our subjects.

The presence of a *Q wave in the precordial sternal derivation* is emphasized by Mortensen[20b] as the most frequent and most characteristic change in the QRS complex in cases of anterior cardiac infarction. In normal persons Mortensen has never seen a Q wave in the sternal derivation employed by him, namely, CF_2 (from the left sternal margin in the fourth intercostal space to the left leg). In Lead *d* we found a Q wave in eleven of our 100 normal subjects; the largest Q wave was 1.2 mm. Therefore, we have to conclude that in Lead *d* the Q wave must measure at least 2 mm. in order to be designated as abnormal. It may be added that Holzmann[8] states that a T wave in the derivation from the left sternal margin, at the attachment of the fifth rib, to the left leg, is not pathologic.

THE S-T SEGMENT

In a great majority of the records the S-T segment was slanting upward (Table VII), and very frequently its transition into the ascending branch of the T wave was very gradual, so that it was impossible to locate the end of the S-T segment and the beginning of the T wave. In other cases the rise of the curve was accentuated, and the accentuation presumably corresponded to the beginning of the T wave. A saddle-shaped S-T segment occurred ten times in Lead *s*—in seven of these records together with a "second R wave," and three times in connection

with absence of the S wave. In Lead *d* the S-T segment was saddle-shaped in only one subject, in whose record there was a small, notched S wave.

TABLE VII

THE S-T SEGMENT

	LEAD		
	d	*s*	II
Course			
Horizontal (no. of subjects)	1	1	12
Rising (no. of subjects)	98	89	75
Falling (no. of subjects)	0	0	0
Saddle-shaped (no. of subjects)	1	10	13
Isoelectric (no. of subjects)	5	18	36
Above isoelectric line (no. of subjects)	87	65	44
Maximal elevation (mm.)	2.8	2.4	0.9
Below isoelectric line (no. of subjects)	8	17	20
Maximal depression (mm.)	0.2	0.8	0.5

In measurements taken 0.05 sec. after the end of the QRS complex, the level of the S-T segment was above the isoelectric line in eighty-seven subjects in Lead *d*, and in sixty-five subjects in Lead *s;* the maximal elevation was 2.8 mm. in Lead *d*, and 2.4 mm. in Lead *s*. The S-T segment was found below the isoelectric line, but sloping upward, eight times in Lead *d* and seventeen times in Lead *s;* the maximal depression occurred in Lead *s*, and amounted to 0.8 mm. Therefore, when the level of the S-T segment is 1 mm. or more below the isoelectric line, it may be designated as abnormal, and, likewise, if the level of the S-T segment is 3 mm. or more above the isoelectric line. But, as in the extremity derivations, it is doubtful whether an abnormally high level of the S-T segment is of any pathologic significance in cases in which the form of the S-T segment is normal.

If in the precordial leads we establish the isoelectric line as a horizontal line through the P-Q segment, we have to require that the S-T level fall 1 mm. or more below this line in order to be able to characterize the course of the S-T segment as abnormally negative. Since the P-Q segment in Leads *d* and *s* often falls below the isoelectric line proper, we will thus be unable to make the diagnosis of "abnormally negative S-T segment" in several of those cases in which the S-T level is from 1 to 1.8 mm. below the true isoelectric line, and in which the P-Q level at the same time is negative (cf. the preceding paper on the extremity derivations[14]).

THE T WAVE

In both Lead *d* and Lead *s*, the T wave was positive in all of the 100 subjects, and took the form of a gradual, smooth curve; the higher this wave, the more pointed was its form. An exception to this rule occurred in two cases in Lead *d*, in which the highest part of the curve formed a plateau (the precordial derivation from one of these subjects is shown

in Fig. 1B). (In a few normal persons, who are not included in this series, we have seen a little depression in the middle of the plateau here described, so that the T wave in these cases had a two-humped appearance.)

TABLE VIII

THE T WAVE

	LEAD		
	d	*s*	II
Form			
Positive (no. of subjects)	100	100	100
Size (mm.)			
Minimum	0.9	1.3	1.1
Maximum	10.6	19.2	5.8
Av.	4.5	7.1	3.0
10 mm. or more (no. of subjects)	1	14	
Less than 1 mm. (no. of subjects)	2	0	

In Lead *d* the average size of the T wave was 4.5 mm.; in Lead *s* it was 7.1 mm. In two subjects the T wave in Lead *d* measured only 0.9 mm. The smallest T wave in Lead *s* was 1.3 mm. Hence a T wave smaller than 1 mm. will always be suspect; and diphasic and negative T waves (in these age classes) are always abnormal. The dispersion for the T wave in Lead *d* was 2.3 mm.; in Lead *s* it was 3.0 mm. Therefore, the limit for the normal height of the T wave in Lead *d* may be set at 12 mm., and in Lead *s* at 17 mm. In our series these limits were exceeded only once, namely, in Case 25 (man, aged 41) in which the T wave in Lead *s* measured 19.2 mm. in height; the next in height, in Lead *s*, measured 13.4 and 13.0 mm. Most other investigators (e.g., Katz and Kissin,[10] Wood and Wolferth,[31] and Holzmann[8]) set the limit for the normal height of the T wave at 9 or 10 mm. In fourteen of our subjects the T wave in Lead *s* measured more than 10 mm., and in one of these the T wave was higher than 10 mm. in Lead *d*, also.

THE Q-T INTERVAL

For the normal duration of the Q-T interval in Lead II, Larsen and Skúlason[14] have derived the following formula: $Q\text{-}T = \frac{1}{8}\ R\text{-}R + 0.28 \pm 0.05$ sec., in which Q-T and R-R stand for the average duration of the Q-T and R-R intervals in seconds. Analysis shows that this formula is applicable also to Lead *d* and Lead *s*.

SEX AND AGE DIFFERENCES

The investigation of this question was carried out for these derivations in the same manner as for the limb leads.[14] As is evident from Table IX, the average height of the QRS complex and of the T wave was found to be greater in the men than in the women; likewise, the average duration of the P wave, P-Q interval, and QRS complex was greater in the

men than in the women. Some of the waves showed a statistically significant age difference (indicated by italic figures in Table IX). A statistically significant difference was found also in the S-T level in Lead *s;* this segment was above the isoelectric line more often in men than in women. There was no particular difference between the two age classes.

TABLE IX

SEX AND AGE DIFFERENCES

	MEN	WOMEN	30-40 YEARS	40-50 YEARS
Av. height of waves (mm.)				
R wave in Lead *d*	8.4	6.9	7.6	7.7
S wave in Lead *d*	9.0	6.9	8.2	7.6
"The intrinsic deflection" in Lead *d*	*17.5*	*13.7*	15.7	15.3
T wave in Lead *d*	*6.0*	*3.0*	4.4	4.5
R wave in Lead *s*	*26.7*	*22.1*	23.2	24.7
S wave in Lead *s*	6.6	4.5	6.4	4.7
"The intrinsic deflection" in Lead *s*	*33.3*	*26.6*	29.5	29.4
T wave in Lead *s*	*8.4*	*5.8*	7.2	7.0
Av. duration (sec.) (Lead *d*)				
P wave	0.105	0.101	0.100	0.105
P-Q interval	0.169	0.158	0.162	0.164
QRS complex	0.094	0.086	0.091	0.090
Other components (no. of subjects)				
S-T positive in Lead *s*	*42*	*23*	37	28
"Second R wave" in Lead *s*	6	4	5	5
Saddle-shaped S-T in Lead *s*	5	5	3	7

CORRELATIONS

The correlation between the components of the precordial derivations was studied by means of graphic methods, and, in doubtful cases, by calculation of the correlation coefficient (r).

TABLE X

R-R interval and $(R + S)_d$	$r = + 0.04 \pm 0.100$
R-R interval and $(R + S)_s$	$r = + 0.15 \pm 0.098$
R-R interval and T_d	$r = + 0.59 \pm 0.064$
R-R interval and T_s	$r = + 0.50 \pm 0.075$

The correlations given in Table X were found between the duration of the R-R interval and the size of the "intrinsic deflection" (R + S), and between R-R and the T wave in Leads *d* and *s*.

It will be noticed that a high T wave was more frequent in persons who at rest have a slow pulse rate than in those who at rest have a faster pulse rate. On the other hand, there was no correlation between the size of the intrinsic deflection and the duration of the R-R interval. This confirms our observations on the extremity derivations, namely, that those components of the electrocardiogram which are caused by the contraction of the myocardium are dependent upon the pulse rate to a greater extent than those caused by propagation of the impulse.

Between the size of the components of the QRS complex and the height of the T wave, correlations were found as shown in Table XI.

TABLE XI

R_d and T_d	$r = + 0.15 \pm 0.098$
$(R + S)_d$ and T_d	$r = + 0.40 \pm 0.084$
R_s and T_s	$r = + 0.36 \pm 0.087$
$(R + S)_s$ and T_s	$r = + 0.46 \pm 0.079$
$(R + S)_d$ and $(R + S)_s$	$r = + 0.60 \pm 0.064$
T_d and T_s	$r = + 0.70 \pm 0.051$

Thus, in Leads *d* and *s* there was a positive correlation between large intrinsic deflections and large T waves. On the other hand, in contrast to Lead *s*, Lead *d* showed no correlation between large R waves and large T waves because the S wave in Lead *d*, in contrast to Lead *s*, makes up an essential part of the intrinsic deflection. These studies show that a large QRS complex in the various derivations is associated more often with a large T wave in the same derivations than with a low T wave. The two last coefficients show further that the occurrence of a large QRS complex and a high T wave in one precordial derivation most often will be associated with large waves in the other precordial derivation. That large waves in the precordial derivations most often are associated with large waves in the extremity derivations (at any rate in one of these leads) is evident from the analyses in Table XII.

TABLE XII

Greatest (R + S) in Leads I, II, or III and $(R + S)_s$	$r = + 0.34 \pm 0.088$
Highest T wave in Leads I, II, or III and T_s	$r = + 0.073 \pm 0.047$

We have further sought to find out whether there was any correlation between the size of the waves and the size of the experimental subject, as measured by the body surface, but there was no such correlation (Table XIII). Nor was there any correlation between the size of the waves and excessive weight or less than average weight of the experimental subjects, i.e., their weight in percentage of the normal weight.

TABLE XIII

Body surface and $(R + S)_s$	$r = + 0.16 \pm 0.097$
Body surface and T_s	No correlation (diagram)

DISCUSSION

Shortly before the appearance of the proposal made by the American Heart Association[25, 26] about standardization of precordial leads, Larsen and Warburg[15] had presented the following principle, which they considered the most rational for the connection of the leads in taking a precordial electrocardiogram: *The connection of the leads, the polarity of the galvanometer, and the direction of travel of the photographic*

recording medium should agree mutually in such a way that, when a negative potential is impressed on the exploring electrode, it would be recorded as a downward deflection; the curve would be read from the start (at left) towards the right. This principle is founded partly on the fact that it is in keeping with the general principles for graphic recording, and partly on the fact that the nomenclature proposed by Einthoven for derivations from the extremities is, in this way, readily applicable to the precordial leads, also. Both the precordial leads recommended by the American Heart Association and the Leads *d* and *s* which were employed in the present studies are in harmony with the above principle. The most important practical result of this is that persons who have positive P and T waves in Leads I and II usually will have positive P and T waves in the precordial leads, so that one avoids the "mirror-reflected" electrocardiograms which were obtained with the "older" connection of the leads (cf., for instance, Wolferth and Wood[29]).

The American Heart Association did not wish to make any final decision as to the location of the indifferent electrode. Most examiners now apply the electrode to either the left leg or the right arm. As is evident from the studies reported by Shipley and Hallaran,[23] Sorsky and Wood,[24] and Edwards and Vander Veer,[1] pairing the precordial electrode with one on the left leg in normal, adult subjects gives either positive, diphasic, or negative P waves, and, also, but only in the sternal *d*-like derivations, either positive, diphasic, or negative T waves. The significance of the T wave in such derivations is therefore reduced greatly, i.e., it is limited chiefly to those changes that appear during the observation of the patient. In contrast thereto, a diphasic or negative T wave (and P wave) in a derivation from the precordium to the right arm is always abnormal (in adults). In our opinion, this difference shows conclusively that it is preferable to place the indifferent electrode on the right arm, rather than on the left leg.

As to the location of the exploring electrode, it is to be mentioned that an increasing number of examiners prefer and recommend the employment of at least two precordial leads, namely, one from the left side of the heart and one from the right side (Groedel,[4] Roth,[22] Holzmann,[8] Freundlich and Lepeschkin,[2] Mortensen,[20a] Robinson, Contratto, and Levine,[21] and Wood and Selzer[32]). We have selected Lead *d* and Lead *s* because Groedel's investigations suggest that Lead *d*, particularly, will give information about the condition of the right ventricle, and Lead *s*, particularly, about the condition of the left ventricle. Groedel and Koch[6] have shown that a potential maximum for the intrinsic deflection corresponding to the right ventricle is found at the xiphoid process, and that the corresponding potential maximum for the left ventricle is located a few centimeters lateral to the apex of the heart. Therefore, the sites of derivation from the precordium should

vary according to the position of the heart. This applies in particular to Lead *s;* it may be justifiable to let the site of derivation for Lead *d* be determined by the external topographic landmarks, for the location of the right ventricle is far less variable than that of the left ventricle under pathologic conditions. Whether there is any reason to prefer Leads *d* and *s* to the leads recommended by the American Heart Association—Leads CR_2 and IVR (see the introduction)—is a question we cannot yet decide; at present, members of our department are collecting material to elucidate this question. Still, it may be mentioned now that Lead *s* offers one advantage over Lead IVR, for Larsen[13] and Roth[22] have shown that derivations in which the exploring electrode is located a little outside the apex of the heart are easier to reproduce than derivations in which the exploring electrode is placed just over the apex of the heart.

SUMMARY

The present work is an analysis of precordial derivations *d* and *s* from 100 normal subjects (fifty women and fifty men), whose ages ranged from 30 to 50 years. In Lead *d* the exploring electrode is placed so that its center is located at the apex of the angle between the left costal margin and the xiphoid process. In Lead *s* the exploring electrode is placed so that its center is located 4 cm. to the left of the apex of the heart, and at the level of the apex. In both of these leads the electrode on the right arm serves as the indifferent one. "Modern" connection of the leads is employed. The more important results are evident from the tables.

REFERENCES

1. Edwards, J. C., and Vander Veer, J. B.: Am. Heart J. **16**: 431, 1938.
2. Freundlich, J., and Lepeschkin, E.: Cardiologia **3**: 331, 1939.
3. Goldbloom, A. A.: Am. J. M. Sc. **187**: 489, 1934.
4. Groedel, F. M.: Das Extremitäten-, Thorax- und Partialelektrokardiogramm des Menschen, Dresden and Leipzig, 1934, Theodor Steinkopff.
5. Groedel, F. M.: Cardiologia **3**: 23, 1939.
6. Groedel, F. M., and Koch, E.: Ztschr. f. Kreislaufforsch. **26**: 18, 1934.
7. Hoffman, A. M., and Delong, E.: Arch. Int. Med. **51**: 947, 1933 (I).
8. Holzmann, M.: Arch. f. Kreislaufforsch. **1**: 2, 1937.
9. Hoskin, J., and Jonescu, P.: Brit. Heart J. **2**: 33, 1940.
10. Katz, L. N., and Kissin, M.: Am. Heart J. **8**: 595, 1933.
11. Koch, E., and Galli, W.: Ztschr. f. Kreislaufforsch. **26**: 204, 1934.
12. Kossmann, C. E., and Johnston, F. D.: Am. Heart J. **10**: 925, 1935.
13. Larsen, Kaj: Hospitalstidende **79**: 785, 1936; Am. Heart J. **14**: 1, 1937.
14. Larsen, Kaj, and Skúlason, Th.: Am. Heart J. **22**: 625, 1941.
15. Larsen, Kaj, and Warburg, E.: Hospitalstidende **80**: 276, 1937; Am. Heart J. **14**: 7, 1937.
16. Lieberson, A., and Liberson, F.: Ann. Int. Med. **6**: 1315, 1933.
17. Master, A. M.: Am. Heart J. **9**: 511, 1934.
18. Master, A. M., Dack, S., Kalter, H. H., and Jaffe, H. L.: Am. Heart J. **14**: 297, 1937.
19. Mortensen, Vagn: Hospitalstidende **79**: 1233, 1936; Acta med. Scandinav. **92**: 603, 1937.
20. Mortensen, Vagn: Nordisk Medicin, 1939, Vol. II, (a) p. 1971, (b) p. 2749.
21. Robinson, R. W., Contratto, A. W., and Levine, S. A.: Arch. Int. Med. **63**: 711, 1939.

22. Roth, J. R.: Am. Heart J. **10:** 798, 1935.
23. Shipley, R. A., and Hallaran, W. R.: Am. Heart J. **11:** 325, 1936.
24. Sorsky, E., and Wood, P.: Am. Heart J. **13:** 183, 1937.
25. Standardization of Precordial Leads, Am. Heart J. **15:** 107, 1938.
26. Standardization of Precordial Leads: Supplementary Report, Am. Heart J. **15:** 235, 1938.
27. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Am. Heart J. **9:** 447, 1934.
28. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L.: Heart **16:** 155, 1933.
29. Wolferth, C. C., and Wood, F. C.: Am. J. M. Sc. **183:** 30, 1932.
30. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Arch. Int. Med. **52:** 752, 1933 (II).
31. Wood, F. C., and Wolferth, C. C.: Am. Heart J. **9:** 706, 1934.
32. Wood, P., and Selzer, A.: Brit. Heart J. **1:** 49, 1939.

THE SIGNIFICANCE OF THE TENSILITY OF THE AORTA AS AN INDEX OF THE AGING PROCESS IN THE ANIMAL BODY

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IN AN earlier communication, one of the authors (Hume[1]) reported a new procedure for measuring the tensility of the aorta of the rat. Evidence was presented indicating the value of this test as a measure of the normal aging process in the animal organism and of various environmental factors influencing that process.

In these experiments the Hume tensometer apparatus, which applies a gradually increasing stress to a 1 cm. ring of the aorta, was used to record the association between force applied and amount of stretch. From these observations Young's modulus of elasticity could be computed for each degree of stress, and a curve constructed relating the change in the value of the modulus to change in stress. Since the experiments proceeded from zero tension to the breaking point with each aorta ring, no measurement of elasticity (in the sense of an ability to regain an original length after stretching) was involved. The results were expressed in terms of the modulus, principally because rates of change in stretch and stress gave a clearer picture of tensile behavior than absolute values.

In general, all aortas gave a characteristic curve when the moduli for successive points were plotted against the successive stresses at these points, as observed during progressive stress. The tensile resistance at first decreased to a minimum point (loads from zero to 54 Gm.). This decrease is probably related to the normal elasticity of the wall. Further increase in stress led to a progressive increase in tensile resistance in a practically linear manner, until the point of rupture. Although there were interesting differences in the initial limb of the curve and in the points of inflection in different experimental groups, the groups were most strikingly distinguished by the slope of the long ascending limb, and, in some instances, by the ultimate tensile strength (weight supported at point of rupture).

The earlier data for individual groups indicated that both increasing age and higher environmental temperatures decreased the ability of the

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aorta to resist distention stresses. Both alcohol and lead intoxication increased tensile resistance slightly above the values obtained for the control group, a result which, in the alcohol group, was associated with retarded growth.

The authors are well aware that the above conclusions were based upon a technique which does not duplicate the stress conditions of normal function, either in regard to the mode in which force is applied or the absolute values for the force. In this sense the method is distinct from that employed in investigations in which hydrostatic pressure has been applied to distend arterial sections,[2] or in which the factor of elasticity has been studied with forces largely within the range of physiologic values.[3] A physically determined index of tensility yields, however, a very precise picture, and the results discussed above strongly suggest that the structural factor which was measured is responsive to several important environmental variables. For this reason the present experiments were planned to check the above conclusions on age and temperature, and have been extended to two new variables, namely, (1) the effect of a continuing environmental disturbance of the nervous system and (2) the ingestion of thyroid extract.

APPARATUS AND TECHNIQUE

No change was made in the tensometer, which was fully described in a previous publication.[1] Groups of forty animals were exposed to temperatures of 65° F., 83° F., and 95° F. in group cages provided with temperature regulation. When temperature was not an experimental variable, the cage temperature was held at 83° F. The animals were male albino rats from a common source, and their experimental exposures were begun when they were 60 days old. Fifty per cent of each group were sacrificed at the age of 120 days and 210 days, respectively. Since the groups were started serially at approximately weekly intervals, it was possible to equate the mean initial weights within narrow limits. Animals were weighed at weekly intervals, and mean growth curves were computed. In all cases a standard ration was fed, except in the case of the "thyroid" group, in which this ration was supplemented with 0.6 Gm. of desiccated thyroid (Lilly, U.S.P. Thyroid) per 1,000 Gm. of basic ration. One gram of this desiccated thyroid preparation is equivalent to 5 Gm. of fresh thyroid. The proportion of thyroid to food was 0.06 per cent by weight.

In order to obtain a disturbing feature in the temperature-controlled cage of the "disturbed" group, a telechron-controlled switching box was constructed which produced at set intervals a series of exciting stimuli. These were three in number, and included a ringing bell, vibration and noise, and a sudden blast of air. During each hour a sixteen-minute period of disturbance was produced. This consisted at first of a bell ringing (ten minutes), vibration and noise (five minutes), and a blast of air at high velocity (one minute). The order and length of time of these stimuli were varied from time to time in order to prevent conditioning to any one combination of disturbances. The bell was an ordinary door bell; the blower was of the centrifugal type, and delivered about 150 cubic feet per minute. Vibration and noise were produced by mounting an ⅛ horsepower electric motor, provided with an

eccentric shaft, on a galvanized sheet at one end of the inner cage. Rotation of this shaft at the rate of about 120 revolutions a minute produced a thumping noise and a violent "shimmy" in the cage.

PLAN OF EXPERIMENTS

1939

Five groups of male albino rats, aged 60 days at the beginning of the experiments, were used. Each group consisted of forty-five animals; twenty were sacrificed at 120 days and twenty at 210 days, allowing a margin of five to take care of any mortalities suffered by the group. The five groups were scheduled as shown in Table I.

TABLE I

EXPERIMENT NO.	13 AND 18	12 AND 17	10 AND 15	11 AND 16	9 AND 14
Treatment	Disturbed	Thyroid*	Normal control	High temperature	Low temperature
Temperature (°F.)	83	83	83	95	65
Entered cages	4/14	4/21	4/28	5/5	5/12
Sacrificed, first 20	6/13-14	6/20-21	6/27-28	7/4-5	7/11-12
Sacrificed, second 20	9/11-12	9/18-19	9/25-26	10/2-3	10/9-10

*0.06 per cent, desiccated, in diet.

Several days of physiologic conditioning were allowed for the 65° F. and 95° F. groups, while the temperatures were gradually lowered or raised. A chart for daily temperature readings was attached to each cage, with space for a recording of the total weight of the animals in each cage at weekly intervals. Particular care was taken to see that the thyroid and 95° groups had sufficient water at all times. All groups received the standard Bal-O-Ration diet ad lib.

1940

Three groups of male albino rats, aged 60 days at the beginning of the experiments, were used. Each experiment ran for sixty days, so that at the time of sacrifice these animals were 120 days old. The schedule of experiments is given in Table II.

TABLE II

EXPERIMENT NO.	21	20	19
Treatment	Disturbed	Normal controls	Low temperature
Temperature (° F.)	83	83	65
Entered cages	3/11	3/13	3/15
Sacrificed	5/13-14	5/15-16	5/17-18

At the time of sacrifice an aorta ring from each rat was preserved for section and histologic examination, in addition to the section used for stretching. The following structures were also removed and fixed for later study: (1) heart, (2) liver, (3) testes (weighed together), (4) pituitary, (5) adrenals (weighed together), and (6) prostate and seminal vesicles (weighed together). The results of the examination of these tissues will be reported in a later paper.

RESULTS

Perhaps the most general evaluation of the tensility factor can be obtained from a comparison of curves for various treatments and ages in

relation to the mean curve for all experiments over the three years of work. Fig. 1 is a master graph which contrasts the following curves: A_1, the mean curve for all groups, regardless of age or treatment (1939-1940); A_2, the same as A_1, but including also 1937 and 1938; *B*, for all groups exposed to low temperature, regardless of age; *C*, for all groups at moderate temperatures, regardless of age; *D*, for all groups at high temperature, regardless of age; *E*, for all groups at 120 days of age, regardless of treatment; and *F*, for all groups at 210 days of age, regardless of treatment. Although a statistical assessment must be made of the reliability of these apparent differences, some orderly relation must appear in such a graph if age and treatment have had a positive effect. The ordinate value "E" represents a modulus of elasticity, and is computed from the following formula:

$$E = \frac{F}{a} \cdot \frac{L}{dl}$$

in which

F = force applied,
a = area cross section,
L = original length,
dl = change in length.

In earlier experiments,[1] groups exposed to a low environmental temperature gave a tensility curve which was strikingly different from that of other groups, and was in the direction of the high tensile resistance which was found to be typical of young animals. In Fig. 1, curve *B*, which includes three other groups raised at 65° F., we observe this effect again, indicating a higher tensile resistance for the 65° group than for any other.

Below curve A_2, the grand average of *all* experiments, we find the mean curves for all other groups. In point of placement on the graph, we find that the addition of three groups to the original moderate-temperature experiments, and of two groups to the high-temperature experiments, results in a descending order for curves *B*, *C*, *D* (low, moderate, and high temperature), in which tensile resistance decreases as the temperature increases. These graphic separations have been statistically assessed by two methods; both methods were applied to the ascending limb of the curves. The first analysis consisted of testing the variance within each experiment due to individual regressions against the variance between experiments from average regression. Snedecor's F test, based on Fisher's Z test, was used as the criterion for significance of variance between trends of curves. The second analysis consisted of testing the significance of difference between mean E's by the same test.

In Fig. 1 a gross age comparison is also presented. Curves *E* and *F* are, respectively, the mean curves for all animals 120 and 210 days old,

regardless of temperature exposure or other treatment. Although the separation is less striking we find again that the addition of eight groups 120 days* old and five groups 210 days old to the earlier data has sustained the original conclusion that increasing age is associated with decreasing tensile resistance in aortic rings. The comparison between 120-day and 210-day groups of any one year reveals separate and distinct curves, with a slight overlapping of the most easily stretched young aortas and the least easily stretched older aortas. Statistical tests of differences between the means of the 120-day and 210-day groups proved significant or highly significant except for the "disturbed" groups. Likewise, the differences between the regressions of these same groups showed significant differences except for the "thyroid" and "disturbed" groups. The 95° F. groups were on the border line.

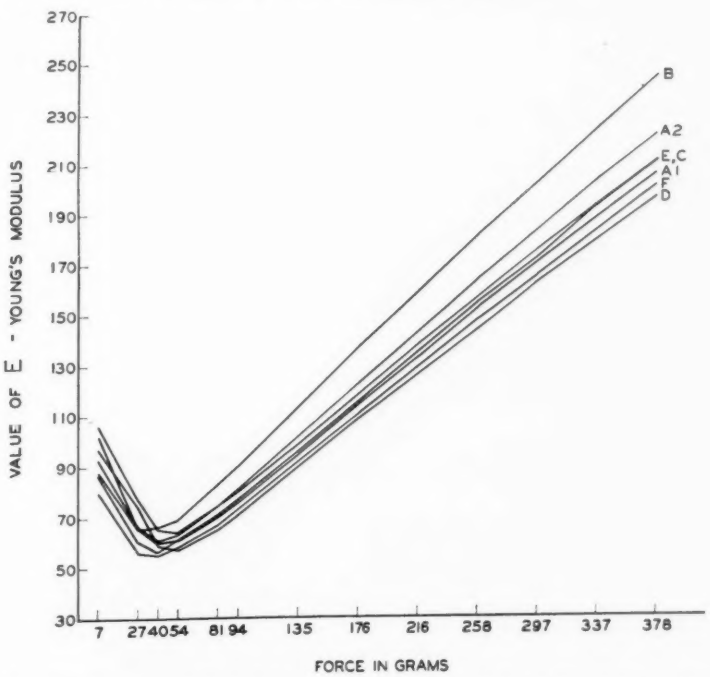

Fig. 1.—Graph of average curves *B*, for all observations at low temperature, irrespective of age; A_2, for *all* observations made, including the 1937-1938 data; *E*, for all observations made on animals 120 days of age, regardless of treatment; *C*, for all observations made at medium temperature, regardless of age; A_1 for all observations made during 1939 and 1940; *F*, for all observations made on animals 210 days old, regardless of treatment; and *D*, for all observations at high temperature, irrespective of age.

The question now arises as to the extent to which these general statistical conclusions can be supported by the curves for temperature at a given age and for age at a given temperature. In Fig. 2 the mean tensility curves for all groups at the standard age of 120 days have been

*There were *no* 120-day groups in the earlier data.

plotted. Curves for the "disturbed" and thyroid-fed groups have been included for this age, but the immediate comparison of importance involves the three temperature curves. Even casual inspection of these tensility curves shows that the general conclusion as to the temperature effect on tensility is further supported by data obtained when age is experimentally constant at 120 days. Statistical tests of this graphic separation show that there is a highly significant difference between the regressions of each group except the 95° F. and the "thyroid" groups of 1939.

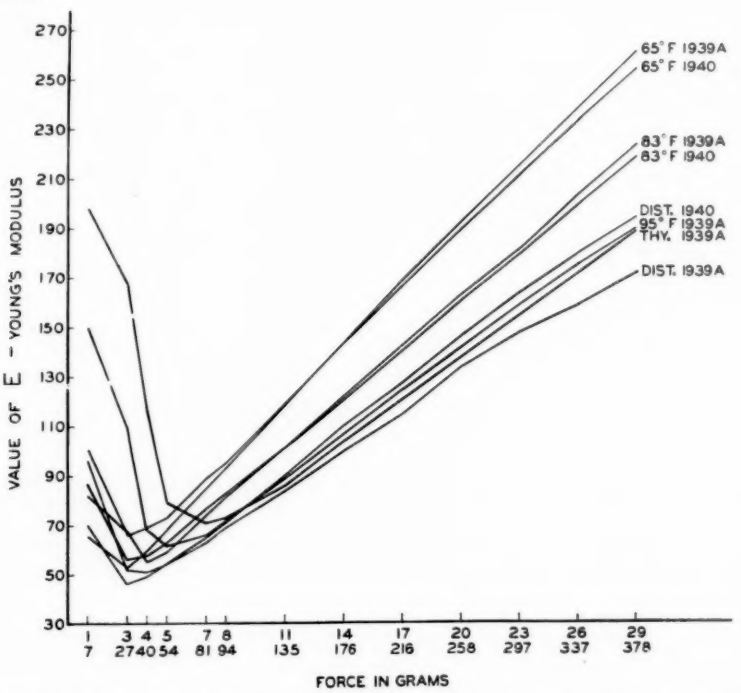

Fig. 2.—Graph of 120-day observations, showing the effects of different treatments at one given age.

In comparing the means of these eight 120-day groups, a highly significant difference was found between the temperature groups. However, no significant difference was found between the 95° F. and "thyroid," the 95° F. and "disturbed," and the "thyroid" and disturbed" groups of 1939. To strengthen the evidence, there was no significant difference between the 65° F. experiments done in 1939 and 1940, the 83° F. experiments of 1939 and 1940, and the "disturbed" experiments of the two years.

In Fig. 3 a similar comparison of temperature effects has been made for the standard age of 210 days. The inverse correlation of tensile resistance with environmental temperature is not perfect for the data as a whole at the age of 210 days. Analysis of the results by years

shows that in the original experiments the clearest association of temperature was with high tensile resistance in the low temperature group, and with lower tensile resistance in the moderate and high groups. The means of the two latter were not significantly different. In the experiments done in 1939, the order confirms perfectly the effect noted at the age of 120 days. It should be pointed out, however, that a 5° higher temperature was used in the hot cages and also that the 1939 curves are all placed somewhat lower than those for 1937-1938. The true explanation of this latter effect is not known. It may have been the result of obtaining animals from a different source, which seemed advisable because a number of animals received from the first source at the beginning of one unfinished series were thought to be infected with middle ear disease. These were destroyed and a new source used. In any event, we find that a combination of the two curves for low, medium, and high temperatures, respectively, in this series, gives a clear separation between the low temperature and the medium and high, with only a small difference between medium and high groups. This was noted in the original study.[1]

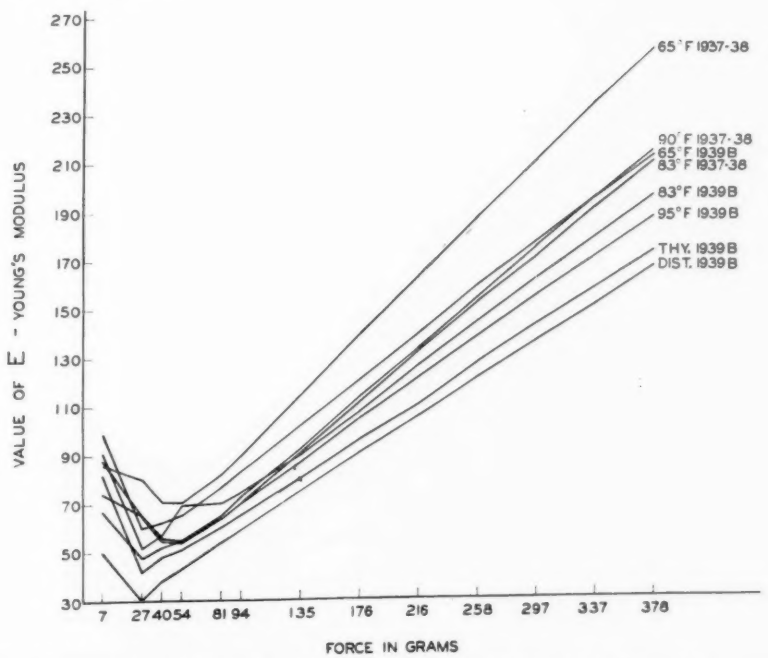

Fig. 3.—Graph of the 210-day observations, showing the effects of different treatments at a given age of 210 days.

In similar manner, a more refined estimate of the effects of age, independent of temperature, may be gained through a study of Fig. 4. Here the curves for the three temperature groups have been plotted, and

the age noted opposite the individual temperature curves. A separation between years in which the experiments were performed is apparent here, as well as in the temperature effects at the age of 210 days. The principal conclusion, however, that for a standard temperature tensile resistance decreases with increasing age, is still borne out. For four groups at 65° F., four at 83° F., and two at 95° F., we find within each separate temperature group a lower mean tensile resistance for the older groups (marked B). The trend of all experiments, regardless of series, justifies this conclusion. Statistically, however, it is probably most sensible to test the age hypothesis within a single year's series. For example, we find that in the 65° F. group in 1939, the 120- and 210-day subgroups differ significantly from each other, both as to regression and as to mean.

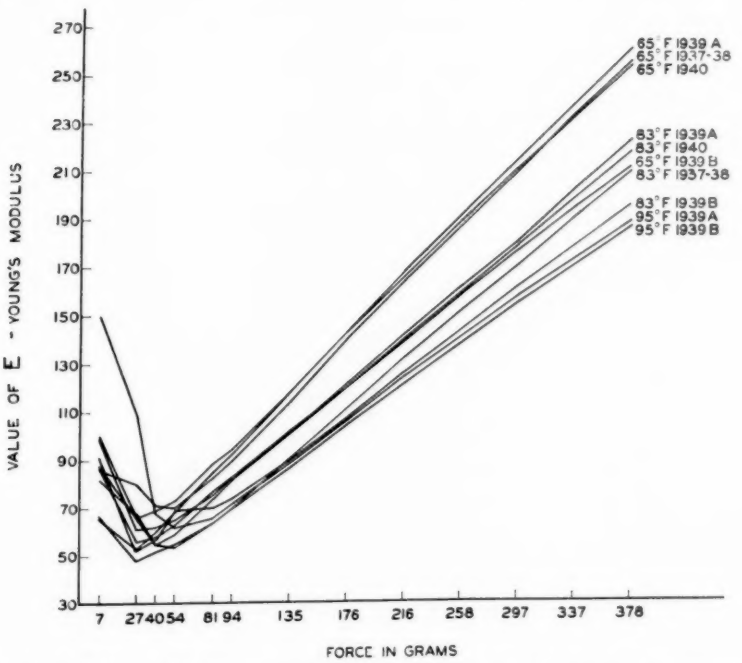

Fig. 4.—Graph of the observations after 65° F., 83° F., and 95° F. treatments. All the curves marked 1939A are from rats 120 days old; all the curves labeled 1939B are from rats 210 days old; and all the 1940 observations were made on rats 120 days old.

In the 83° F. group of 1939, the 120- and 210-day subgroups also have significantly different regressions and means. Statistically, the significance is not so great as for the pair of 65° F. observations.

In the 95° F. group of 1939, the 120- and 210-day subgroups show significant differences in means and regressions, but these differences are not so significant as the age differences within the 83° F. group, and, of course, not nearly so significant as the differences for the 65° F. observations.

As an approach to the constitutional factor which may have been introduced between the 1937-1938 experiments and those that follow, it is reasonable to ask how significantly different are 120-day groups at the same temperature in two different years if the stock is unchanged. Three comparisons are available, the 65° F. and 120-day groups for 1939 and 1940, the 83° F. and 120-day groups for 1939 and 1940, and the "disturbed" and 120-day groups for 1939 and 1940. With the same strain of animals and standard treatment for a standard length of time, these curves show the following statistical differences:

1. Means are not significantly different; regressions do differ for 65° F., 1939, 1940.

2. Means are not significantly different; regressions do differ for 83° F., 1939, 1940.

3. Means are not significantly different; regressions do *not* differ for "disturbed," 1939, 1940.

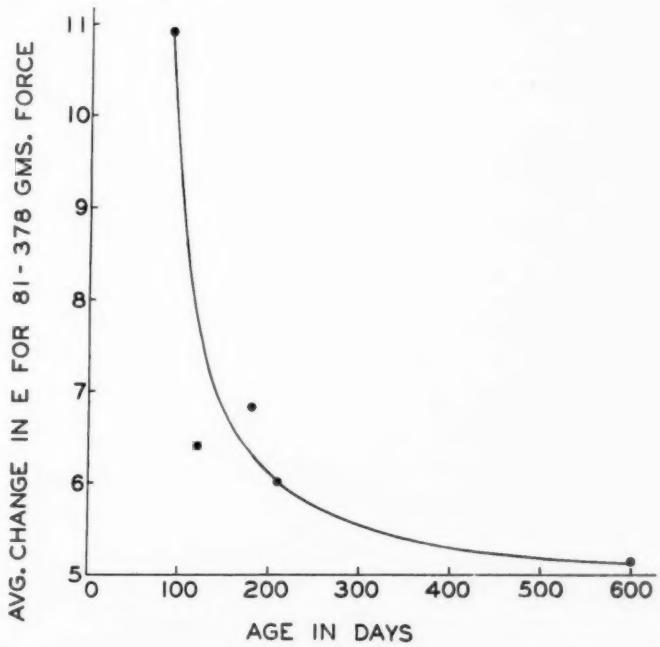

Fig. 5.—Graph of the rate of change in tensile resistance for the ascending limb of the tensility curve. The five points represent data from groups aged 90 days, 120 days, 180 days, 210 days, and 600 days. All five groups were maintained at a temperature of 82° to 84° F.

Obviously, the effect of temperature at a standard age, or of age at a standard temperature, is of a much greater order than group variability from year to year, except in the case of the age effect at high temperature, and the differential effect of medium and high temperatures at the older age of 210 days.

Such a result is entirely consistent and might be generally stated in this manner. Both age and temperature produce definite effects on the tensility curve. The effect of temperature is most pronounced at the earlier age. At the later age the distinction between high and medium environmental temperatures tends to disappear. The effect of age is most clearly seen at low and medium temperatures, whereas at the higher temperature the age effect is least conspicuous.

In these comparisons it must be remembered that the terms "age" and "temperature" refer to the conditions of these investigations and are not intended as general statements. There is, indeed, evidence from an earlier publication[1] which, in conjunction with the newer studies here reported, indicates that the age decrease in tensile resistance is progressive. In Fig. 5 we have plotted the rate of change for the ascending limb of the tensility curve, versus age in days, for data covering at least two-thirds of the rat's lifetime (90 to 600 days).

It is clear from this figure that tensility is inversely associated with age. We do not, however, know what the effect of prolonging low, medium, and high temperatures beyond 210 days may be. Fig. 5 is based upon data from animals which lived at or near the point of thermal neutrality for rats (82° to 84° F.). Since temperature has a substantial effect upon the growth of the rat, there seems to be a reason for relating the temperature effects up to the age of 210 days to general growth effects. Factors inhibiting growth (cold, alcohol) have been found to produce animals whose tensility curves resemble those of younger animals. Whether or not temperature effects may still be seen in tensility curves from animals who have attained their maximal growth, although at different rates, must be settled by further work.

Effect of Thyroid Feeding.—Any attempt to gain insight into the factors responsible for the effect of age and temperature on tensile resistance must immediately consider the rate of metabolism. It is well known that the metabolic rate of the rat is increased by temperatures either above or below the point of thermal neutrality, and that, in a gross sense, any age effect is also broadly associated with total cumulative metabolism, or rather, the sum of "rates of living" which have occurred in an organism from birth to a given age.

In an earlier paper[1] the effect of high or low temperatures in elevating the rat's rate of metabolism from a level of about 600 cal/M^2/24 hours to approximately 1,000 cal. was mentioned. However, in so far as increased tensile resistance can be considered as a favorable characteristic, the cold environment is favorable and the hot environment is unfavorable. This statement involves the tentative assumption that the decreased tensility as age advances means generally that decreased tensility is "unfavorable."

This most general comparison of cold and hot environments made it clear, and it is not surprising, that the production of a high rate of metabolism by two different means does not necessarily have a common effect on the organism (effect, in this case, being judged by a property of the aorta). In short, a metabolism of the order of 1,000 cal/M^2/24 hours has very different effects, depending upon whether exposure to heat or to cold is the provocative factor.

There is abundant evidence that thyroid function is increased by cold. In the temperature experiments it was reasonable to conclude that such an increase in thyroid function might be associated with cold exposure and that the increase in metabolism in hot environments was associated primarily with increased tissue temperatures. Feeding thyroid to animals exposed to a normal environmental temperature seemed indicated. In this manner, a supermetabolism caused by excess thyroxin could be induced at normal temperatures. Forty animals were fed 0.6 Gm. of desiccated thyroid extract (Lilly, U.S.P.) per 1,000 Gm. of basic ration (0.06 per cent) and maintained at a cage temperature of 83° F. These animals were sacrificed in two groups of twenty, at the age of 120 and 210 days, respectively. In so far as total metabolism is concerned, we were thus afforded a comparison between the effects of an elevated rate of metabolism induced by exposure to heat or cold and by thyroid feeding.

The effect of thyroid feeding on the tensile resistance of the rat's aorta at the age of 120 days is seen in Fig. 3. Here the curve lies below that of all groups, with the exception of the as yet undiscussed "disturbed" group. Statistically, the curve is significantly different in slope from the 65° F., the 83° F., and the "disturbed" groups, but not from the 95° F. group. In testing the means, the thyroid experiment is significantly different from the 65° F. and 83° F. groups, but not from the 95° F. or "disturbed" groups.

When a comparison is made on the 210-day group, we find essentially the same relationship. An increase in metabolism induced by thyroid feeding produces an aorta whose tensile resistance is decreased. This effect is similar to that produced by high environmental temperatures, in contrast to the effect of cold environment temperatures.

The results on thyroid-fed animals are of particular interest, for the decreased tensile resistance is not associated with retarded growth, as was the case with the 95° F. animals. Previously we[1] noted that growth inhibition produced by alcohol intoxication increased tensile resistance, and in these studies high temperature inhibition of growth produced an opposite effect. It must then be clear that the effect on aortic tensile resistance of these various treatments is no simple effect of general growth or elevated metabolism.

Effect of "Disturbance."—It has frequently been said that the "wear and tear" of modern living is related to life in an environment which is abnormally stimulating. One may assume that this statement, if it has any definite hygienic meaning, suggests that "stimulation" refers to neural factors affecting the level of nervous tension and not purposefully related to normal activity and growth.

Although it seems questionable whether or not we are prepared to create for the rat, or for any other animal, an environment in which "overstimulation" is present, in the sense in which we might understand it as a feature of high-pressure urban life, we can easily provide an environment which is noisy and physically unstable. In a previous section the apparatus used to produce noise and vibration was described. Such stimuli are almost universally effective in producing initial alarm reactions in animals. Through variation in the sequence and length of each particular stimulus in the disturbance pattern, an effort was made to provide some degree of continuous novelty in the situation. Observation showed that as far as outward signs (posture and activity) were concerned, the animals apparently adapted within a few days to the disturbing features of the environment. They interrupted their feeding at the beginning of noise or vibration, only to continue after a few moments. With vibration and high velocity of air movement, certain cage locations were "least disturbed," and animals usually congregated at these locations until the disturbance had ceased. At no time, however, could these stimuli be completely escaped in a physical sense, and it is logical to assume that the environment was "disturbed," even though dramatic evidence of such an effect on the animals rather quickly disappeared.

In Figs. 3 and 4 the comparative tensile resistance of aortas from the "disturbed" group is shown for two groups 120 days old, and one group 210 days old. In the first 120- and 210-day groups (1939 A and B) the curves of tensile resistance lie below the curves for all other groups. The change is in the direction of a decreased resistance, and, if we take young animals or animals raised in a cold environment as a reference, in an unfavorable direction. Statistically considered, the regressions of these curves are significantly different (both for 120- and 210-day observations) from any other 1939A or 1939B group, respectively. The analysis of means revels that the "disturbed" 1939A (120 days) differs significantly from the 65° F. and 83° F. groups, but not from the "thyroid" and 95° F. groups of 1939A. At 210 days the mean difference between "disturbed" and any other 1939 group is significant or highly significant.

The results were very surprising, even though the acceptance of curves of lowered tensile resistance as unfavorable is regarded as a tentative conclusion. It is important to state that this conclusion with respect to the effect of disturbance had been reached in the 1939 experi-

ments. In order to check this result prior to publication, a new series was run in 1940 on a new group of animals. These were carried to the age of 120 days, and, in order to establish a reference point in the new series, temperature groups at 65° F. and 83° F. were run concurrently. The results are seen clearly in Fig. 2. The new curves check very well with the previous ones, both with respect to disturbance and temperature. The 1940 curve for the "disturbed" group lies at a slightly higher level than the 1939A curve, but its location in the area which is typical for other "unfavorable" treatments is obvious.

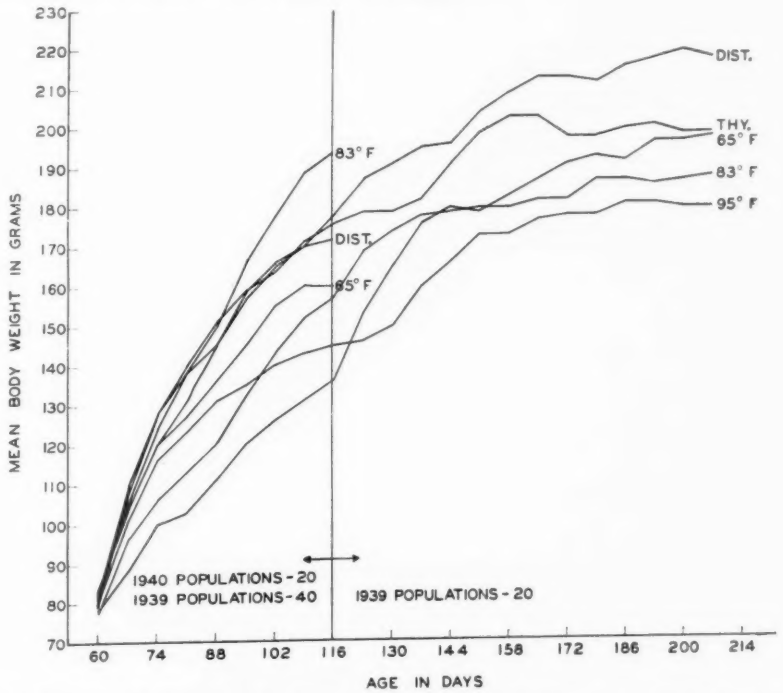

Fig. 6.—Growth curve obtained from weekly weight measurements of all 1939 and 1940 groups. Double arrow indicates age at which twenty animals from each of the 1939 groups were sacrificed.

Effect of Various Treatments on Growth.—A logical analysis of the growth curves obtained from the 1939 and 1940 studies presents several difficulties. The main difficulty lies in the fact that the curves from 60 to 120 days represent the average weight of forty animals, whereas from 120 to 210 days the average weights are based on twenty animals. Thus, there is an increased variability in the second half of the curves which is related to the smaller number of animals. It is clear that, by reducing the crowding of occupants of a cage (from forty to twenty animals), a generally favorable effect has resulted which we had not anticipated. The precise nature of this influence is obscure, for all groups were given an abundance of food. We can avoid any prejudicial

effect of this variable by discussing the two sections of the curves separately. In Fig. 6 the growth curves of all 1939 and 1940 groups are given, after smoothing, with a moving average of three.

In the period from 60 to 117 days it seems improbable that there was any decided difference in growth rate for the three 1939 temperature groups. Such differences as exist suggest that high or moderate temperatures may be advantageous for growth in the early part of the period; this effect becomes less marked as the animal increases in size, and is finally reversed in adulthood. The removal of twenty animals from the cage resulted in an immediate increase in growth rate in the 1939 temperature groups, and the absence of such a marked effect in the "thyroid" and "disturbed" groups suggests that these rapidly growing animals are nearer their physiologic limit of increase, and hence least susceptible to the effect.

We were able to check this "crowding" effect with 1940 data, in which we have the growth curves for twenty animals in the period from 60 to 117 days. As may be readily seen in Fig. 6, these groups grew much more rapidly than the 1939 groups, which comprised forty animals.

In the second age period, 117 to 210 days, the 1939 temperature curves reverse themselves, and, at the final period (210 days), the heaviest animals are those from a cold environment, the lightest, those from the hot environment, and the moderate temperature group occupy the middle rank in weight.

One is tempted to say that in an experiment uncomplicated by any change in cage population, the effect of temperature up to 120 days would probably be a relative inhibition of growth in the cold (see 1940 results also), in contrast with final adult results, in which cold is favorable and heat unfavorable for growth, as measured by weight.

Somewhat to our surprise, the growth curves for the "disturbed" and "thyroid" groups were consistently above the temperature groups, and the crowding effect was not noticeable, either when the cage populations were reduced to twenty, or when the first growth period was checked for the "disturbed" in 1940 with only twenty animals. This suggests that the rates of growth shown for the "disturbed" and "thyroid" were already near a maximum for this strain of rat and the particular diet used.

Both "thyroid" and "disturbed" animals gave group results on the arterial tests in 1939 and 1940 which were "unfavorable"; in other words, in the direction of the effect produced by high temperatures and increasing age. These growth results immediately suggest that perhaps the "thyroid" and "disturbed" were physiologically older as a result of their more rapid growth and that the "unfavorable" arterial performance of these groups was really an age artifact. This conclusion is untenable, however, when it is remembered that the "thyroid" and

TABLE III

1939 GROWTH DATA

1	2	3	4	5	6	7	8	9	10	11
EXPERIMENT NO.	AGE (DAYS)	SPECIAL TREATMENT	AV. FINAL WEIGHT (GM.)	INITIAL WEIGHT (GM.)	AV. GAIN IN WEIGHT (GM.)	AV. GAIN IN WEIGHT 120-210 DAYS (GM.)	WEIGHT-LENGTH RATIO	ORDER OF W/L RATIO	AV. LENGTH (CM.)	AV. GAIN IN LENGTH 120-210 DAYS (CM.)
					60-120 days			*120 days*	*120 days*	
9	120	65° F.	145	72	73		8.80	3	16.7	
10	120	83° F.	155	79	76		8.60	5	18.1	
11	120	95° F.	150	80	70		8.76	4	17.0	
12	120	Thyroid	188	79	109		9.66	1	20.0	
13	120	Disturbed	176	81	95		8.88	2	19.8	
					60-210 days			*210 days*	*210 days*	
14	210	65° F.	217	72	145	72	10.29	2	20.1	3.4
15	210	83° F.	204	79	125	49	10.24	3	19.9	1.8
16	210	95° F.	184	80	104	34	9.48	5	19.4	2.4
17	210	Thyroid	204	79	125	16	9.82	4	20.8	0.8
18	210	Disturbed	223	81	142	47	10.90	1	20.4	0.6

65° F. animals had very nearly the same final growth status and that the arterial results for the "cold" animals were quite in the other direction.

It is probably sufficient to note that conditions which are unfavorable from the standpoint of arterial tests are not necessarily associated with retarded growth. Obviously, the effects are subject to the influence of many variables, and the basic physiologic interrelations are not simple.

Inclusion of length and weight-length ratio adds another dimension to the picture of the effect of the various treatments on growth. This discussion will be limited to the five groups studied in 1939 because of the continuity from 60 days to 210 days. It will be seen from Table III that, at 120 days, the "thyroid" group had attained the greatest length, with the "disturbed," 83° F., 95° F., and 65° F. following behind in that order. At 210 days, "thyroid" and "disturbed" were still the longest animals, but 65° F. had moved up from fifth to third place, 83° F. had moved from third to fourth place, and 95° F. from fourth to fifth place. This shift in order is significant, and will be discussed shortly. At 120 days, "thyroid" had the highest ratio, with "disturbed," 65° F., 95° F., and 83° F. following in descending order. At 210 days the "disturbed" group had the highest ratio, with 65° F., 83° F., "thyroid," and 95° F. in the same order. The treatments to which the animals were exposed are clearly reflected in the length-weight ratio of the different groups; weight alone is an incomplete criterion of growth because length as well as weight is affected by treatment.

A closer analysis reveals that the average length of the "thyroid" group, as might be expected, was greatest both at 120 days and at 210 days. At 120 days, it also had the highest weight-length ratio, which shows that it was also the heaviest group. At 210 days, however, the "thyroid" weight-length ratio had dropped from first to fourth place, indicating that the increment of weight had not kept pace with the increment in length, and that the thyroid treatment was producing proportionately longer, thinner rats. It is startling that, from 60 to 120 days, the "thyroid" animals gained 109 Gm., on the average, whereas from 120 to 210 days the average gain was only 16 Gm. The growth curve corroborates the fact that there was very rapid growth in the first 60 days of treatment, with a decided slowing down in the next 120 days. The increase in length from 120 to 210 days seems very small (8 mm.), but it is actually a little in excess of the comparative figures given by Donaldson for change in length with change in body weight.

The "disturbed" animals, at 120 days, had the second highest weight-length ratio, and were the second longest. Therefore, they were also the second heaviest. At 210 days the weight-length ratio was highest, although the length remained in second place. Therefore, the gain in

weight was greater than the gain in length. From 60 to 120 days the average gain in weight was 95 Gm., as compared to 109 for the "thyroid." The contrast between the two groups came in the weight gain attained between 120 and 210 days. Although the "thyroid" gained but 16 Gm. on the average, the "disturbed" gained 47 Gm. In length, the "disturbed," like the "thyroid," gained very little from 120 to 210 days. Most of the weight and length growth in both of these groups was attained early, i.e., between 60 to 120 days.

The three temperature groups behaved somewhat differently. The average gain in weight between 60 and 120 days for the 65° F. group was 73 Gm., which is considerably less than the gain made by either the "thyroid" or "disturbed" groups for the same period, but the gain between 120 and 210 days amounted to 72 Gm. Thus, the total weight gain from 60 to 210 days was slightly more than for any other group, but the important difference is that it was evenly distributed over the period from 60 to 210 days. The weight-length ratio for the 65° F. group at 120 days was third highest; these animals showed the shortest lengths of any group. At 210 days the weight-length ratio had moved up to second place, and the length was also increasing. Thus, the growth of the 65° F. groups was one of even, steady gains, both in weight and length. The largest gains of any group from 120 to 210 days in both measurements were attained by this group. The average increase in length between 120 and 210 days was 34 mm.

The 83° F. groups, which served as the controls for all the others, tended to strike a mean between the behavior of the 65° F. and the "thyroid" and "disturbed" groups. At 120 days the weight-length ratio was the smallest, the length was third greatest, and the weight was the third highest of all the groups. At 210 days the weight-length ratio moved up to third place, indicating a somewhat greater increase in weight in proportion to length. The weight gain averaged 76 Gm. for the 60- to 120-day period, and forty-nine for the 120- to 210-day period. The increase in length between 120 and 210 days averaged 18 mm., which amounted to about half of the gain achieved by the 65° F. group, but twice to three times as much as was gained by the "thyroid" and "disturbed" groups, respectively. The effect of an even, medium temperature seemed to combine the effects of stimulation by thyroid feeding and by a cold temperature. There was more gain in weight early in the experiment than in the latter portion; the rate of increase in length continued during this period, but was not out of proportion to the weight gain.

Finally, the effect of a hot environmental temperature was to produce an animal whose length was proportionately greater than its weight at all times. The weight-length ratios at 120 and 210 days were next to smallest and smallest, respectively, of any of the groups. The average

weight gain from 60 to 120 days was 70 Gm., but was only 34 Gm. from 120 to 210 days, whereas the increase in length during the latter period was 24 mm., or next to the highest. Most of the weight gain took place in the early part of the experiment, but the increase in length continued at a high level throughout.

A brief summary of the 1939 growth experience, as judged by weight, length, and weight-length ratios, shows that the treatment to which each group was subjected had a definite effect, not only on the final level reached, but also on the rate of growth during the experiments. As judged by the "final level" criterion, the "disturbed" group was the heaviest and second longest; the "thyroid," the third heaviest and longest; the 65° F. group, the second heaviest and third longest; the 83° F. group, the fourth heaviest and fourth longest; and the 95° F. group, the lightest and shortest. The rates of change indicate that the "thyroid" group did most of its growing between 60 and 120 days, as did the "disturbed" group. Of the three temperature groups, the 65° F. grew more between 120 and 210 days, and the 83° F. and 95° F. followed at a slower pace.

GENERAL DISCUSSION

To supplement the graphs already presented, we have prepared (Table IV) a summary of the outstanding differences in the total of twenty-one experiments which were carried out between 1937 and 1940. The first five columns record the basic variables, i.e., temperature, special treatment, and age of animals for each experiment. The sixth column gives the mean weight of the animals at the close of each experiment, and the last three columns show values for Young's modulus at three significant points. Column 7 is the initial reading, with a weight of only 7 Gm. Column 8 is the average reading (with weights of 27 to 54 Gm.) at the low point of the curve, where the modulus reaches its minimum value. Column 9 is the reading corresponding to a weight-stress of 378 Gm., where the modulus is close to its maximum.

In general, the modulus for comparable conditions (like the ultimate breaking point) was higher in 1937-1938 than in later experiments (this was caused either by a difference in stock or by some unidentified difference in experimental procedure). The change of final modulus (378 Gm.), with age, in this earlier series was from 370 at 90 days to 250 at 180 days and 184 at 600 days (all at 72° to 73° F.). At 210 days the value at 65° F. was higher (257) than at 82° F. or 90° F. (211 to 215). Lead and alcohol exposure at 82° F. seemed, as pointed out in an earlier communication,[1] to be associated with a higher modulus than that characteristic of control animals of the same age at 72° F., or than that of control animals of the same weight after 210 days at 82° F.

TABLE IV

GENERAL SUMMARY

1	2	3	4	5	6	7	8	9
EXPERIMENT NO.	DATE	TEMPERATURE OF CAGE (° F.)	SPECIAL TREATMENT	AGE (DAYS)	AV. WT. ATTAINED AT END OF EXPERIMENT (GM.)	YOUNG'S MODULUS		
						INITIAL (7 GM.)	LOW POINT (AV. 27-54 GM.)	HIGH POINT (378 GM.)
1	1937-38	72-73*		90		178	98	370
2	1937-38	82	Lead	180	256	181	72	291
3	1937-38	72-73*		180	287	127	60	250
4	1937-38	82	Alcohol	180	217	89	60	272
5	1937-38	65		210	193	86	74	257
6	1937-38	90		210	230	88	58	211
7	1937-38	82		210	260	74	59	215
8	1937-38	72-73*		600	400	85	42	184
9	1939A	65		120	145	66	60	262
10	1939A	83		120	155	82	60	224
11	1939A	95		120	150	150	79	190
12	1939A	83	Thyroid	120	188	198	119	189
13	1939A	83	Disturbed	120	176	96	52	172
14	1939B	65		210	217	99	63	213
15	1939B	83		210	204	91	56	197
16	1939B	95		210	184	67	52	188
17	1939B	83	Thyroid	210	204	82	43	174
18	1939B	83	Disturbed	210	223	50	38	168
19	1940	65		120	168	100	69	255
20	1940	83		120	203	87	59	219
21	1940	83	Disturbed	120	170	70	50	195

*Uncontrolled.

The last thirteen experiments, which were conducted in 1939-1940, are mutually comparable, for they were done with animals of uniform stock. They confirm the earlier conclusions that Young's modulus decreases with age, and, at a given age, with an increase in environmental temperature. It is important to know, however, whether the influence of low temperature in maintaining a high value at a given age is due merely to a slowing up of growth processes or to some directly favorable effect upon the state of the arteries. In Fig. 7 we have plotted all the 1939-1940 experiments to show the relation of the modulus value to the mean weight of the animals, irrespective of age. In every case, however, the final point in each curve represents a 210-day group. All other points are for 120-day groups. It will be noted from the graph that all curves show a tendency to fall with increasing age and weight and that, for a given age and weight, the animals which were kept at a temperature of 65° F. showed a higher modulus than those kept at 82° F., whereas the animals kept at 95° F., as well as those overstimulated by thyroid feeding or sensory disturbance, all showed a modulus lower than normal.

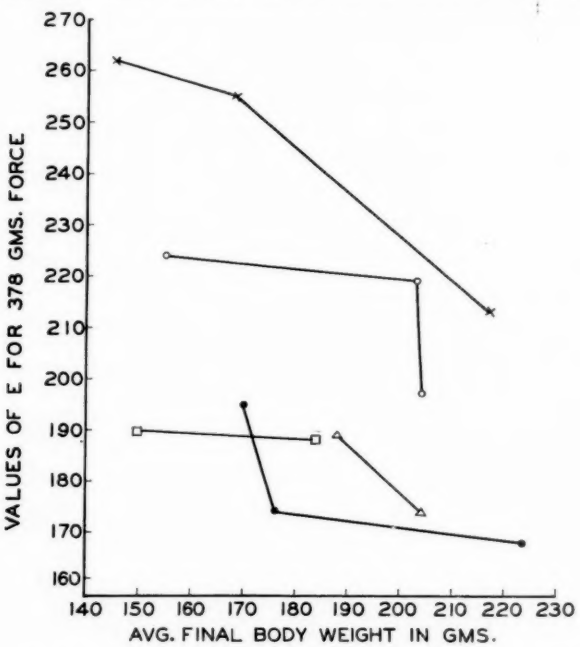

Fig. 7.—Graph of average body weight, versus values of E at a weight of 378 Gm. for various treatment groups, irrespective of age. Crosses (x) are for groups at 65° F.; open circles (o), for groups at 83° F.; open squares (□), for groups at 95° F.; triangles (△), for thyroid-treated groups; solid circles (●), for "disturbed" groups. Points plotted represent both 120- and 210-day results; it so happens, however, that the lowest point in each series is a 210-day group; all other points are for 120 days.

Little has been said about the initial limb of the tensility curve or the low point of the modulus, because it is clear that the slope and placement of the long, ascending, right limb of the curve for a given group

afford the most reliable and characteristic measure of the performance of the artery on the tensometer. Since the stresses involved were well beyond physiologic limits, it is believed that the right limb measures a structural property. It can be seen readily from Table IV, however, that the initial and low modulus values which define the descending curve are, in general, proportional to the final values at 378 Gm. of stress. These initial and low values lie in a stress range which is within physiologic limits. It therefore seems reasonable to conclude that there is a fairly substantial relationship between the structural property, as measured by the ascending limb, and the tensile resistance of the arterial section in the range of physiologic stress which is involved in the initial section of the curve. There are, however, certain rather conspicuous exceptions to the general association between the initial, low, and final values. Groups 11 and 12 (Table IV), respectively the 120-day, 95° F. and 120-day, "thyroid" groups, gave exceptionally high initial values in association with low final values. Both of these groups had experienced rapid early growth, although it should be noted that this tapered off in the 95° F. group between the ages of 80 and 100 days. This is not unusual, for there are sound reasons for believing that the optimal temperatures for growth are higher in the early stages of development than in the later stages. This is shown by the reversal of the position of the growth curves in the 1939 experiments at 88 and 210 days. At 88 days the temperature groups, in the order of greatest weight, were 95°, 83°, and 65° F. At 210 days this order became reversed, and we find the highest level of growth in the 65° F. group, with the 83° and 95° groups following in that order.

Group 9, the 120-day, 65° F. animals, deviated from the general trend of association between initial and final values for the modulus in a direction opposite from that noted for Groups 11 and 12. Group 9 grew more slowly than any other group up to 120 days. These three conspicuous deviations from the general trend may be fortuitous, but it should be noted that these deviations between initial and final values in Table IV concern groups in which conspicuously high or low initial values were associated, respectively, with accelerated or retarded growth at the age of 120 days.

CONCLUSIONS

1. The tensility of the aorta of the rat, as measured by the Hume tensometer, appears to be a valid measure of certain processes of aging in the arterial wall. With advance in both actual and physiologic age (as measured by weight increase), the tensile resistance of the aortic rings to distention stresses shows a progressive decrease.

2. The aortas of rats maintained at an air temperature below normal (65° F.) show a higher tensile resistance than those of rats of the same

age and weight maintained at a temperature of 83° F. This phenomenon is, of course, associated with an increased rate of metabolism.

3. Rats maintained at 95° F., or at 83° F. with regular doses of thyroid extract, show a high metabolic rate which is comparable to that produced by a temperature of 65° F. Yet, in such rats, the tensile resistance of the aorta, instead of being increased, is decreased to a value below that of the 83° F. controls.

4. Rats exposed to repeated sensory disturbances show a similar reduction of tensile resistance; their aortic wall yields to stress more readily than that of control animals of corresponding age and weight, kept at the same normal temperature of 83° F.

REFERENCES

1. Hume, Jean: The Tensility of the Rat's Aorta as Influenced by Age, Environmental Temperature, and Certain Toxic Substances, Am. J. Hyg. **29**: 11, 1939.
2. Fleisch, A.: Structure of Blood Vessels, Bethe Handb. d. normalen u. path. Physiol. **7**: 865, 1927.
3. Clark, J. H.: Elasticity of Veins, Am. J. Physiol. **105**: 418, 1933.
4. Landauer, W.: Thyroid Activity and Environmental Temperature in Frizzle Fowl, Arch. internat. de pharmacodyn. et de thérap. **49**: 130, 1934.

DIGITALIS AND THE NORMAL WORK ELECTROCARDIOGRAM

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DURING the course of routine interpretation of electrocardiograms in this laboratory, the record of a digitalized patient who had undergone an exercise tolerance test was encountered. The record after exercise, but not before, showed depression of the S-T junctions. This was thought to substantiate the clinical diagnosis of angina pectoris. The question was raised, however, as to whether or not digitalization alone might affect the work electrocardiogram, and a search of the literature revealed only one reference to the subject. Zwillinger,[1] in 1935, attempted to correlate the similarity of electrocardiographic changes in cases of digitalized controls with the electrocardiographic changes in subjects with proved coronary artery sclerosis during attacks of angina pectoris. He took electrocardiograms of four young, normal adults before and after exercise and repeated the test after digitalization. He noted that the administration of digitalis produced in some cases a work electrocardiogram with depression of the level of the S-T take-off. The resulting electrocardiograms resembled those from patients during attacks of angina pectoris, although Zwillinger's subjects were normal.

This is an important observation. Furthermore, since this was the only report we could find in either American or foreign journals, and since Zwillinger's observations were made on only a small number of subjects (four), it was considered of interest to repeat the work.

METHOD

Fourteen volunteers were used in the experiment. All were males, and the ages of thirteen of them ranged from 25 to 31 years; the fourteenth was 51 years of age. All were in good health so far as could be ascertained.

An electrocardiogram was made of each subject while at rest. He was then asked to make 100 trips over two steps. Each of these steps was 9 inches high, and a trip consisted of climbing the two steps to a small platform and then descending the opposite side. The subject then faced about, reclimbed and redescended the steps, making a second trip—and so on, until 100 trips were completed without rest. He proceeded at his own rate. Immediately after completion of the 100 trips, a second electrocardiogram was taken. The subject was then digitalized, and the process was repeated.

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TABLE 1

EFFECT OF EXERCISE ON LEVEL OF S-T JUNCTION

NO.	SUBJECT	BEFORE DIGITALIS				AFTER DIGITALIS			
		I	II	III	IV	I	II	III	IV
1	H. F.	0 to +	0 to 0	− to − −	+ to ++	0 to 0	− to − −	− to − −	0 to 0
2	S. R.	0 to 0	+ to 0	+ to −	++ to +	0 to 0	0 to −	0 to −	+ to 0
3	W. M.	0 to −	− to − −	− to −	+ to 0	0 to −	− to −	− to − −	0 to 0
4	M. B.	− to − −	0 to −	+ to 0	0 to +	− to −	− to − −	0 to −	− to − −
5	K. R.	+ to 0	++ to +	+ to +	++ to +	0 to −	+ to −	+ to −	+ to 0
6	I. L.	+ to 0	+ to 0	0 to 0	+ to +	+ to −	+ to −	0 to −	+ to −
7	L. B.	0 to 0	+ to −	0 to −	+ to −	0 to −	0 to −	0 to −	+ to −
8	R. G.	0 to 0	0 to 0	0 to 0	+ to +	0 to 0	+ to 0	0 to 0	0 to 0
9	H. P.	0 to −	0 to −	0 to −	+ to −	− to − −	0 to −	0 to −	0 to −
10	J. M.	+ to 0	+ to 0	0 to 0	+ to +	+ to 0	0 to −	0 to −	++ to +
11	C. B.	0 to 0	0 to 0	0 to 0	0 to 0	− to − −	0 to −	+ to +	− to − −
12	W. P.	0 to 0	+ to 0	+ to 0	0 to 0	0 to 0	0 to −	+ to −	− to − −
13	A. P.	0 to 0	0 to 0	0 to 0	++ to +	0 to −	+ to 0	0 to +	+ to 0
14	R. E.	0 to 0	+ to 0	0 to −	++ to +	0 to 0	0 to −	+ to −	+ to −

The subjects were digitalized by the administration of 0.1 Gm. tablets of digitalis folia. The individual total doses ranged from 1.5 to 3.4 Gm., and the time consumed in effecting digitalization, in thirteen cases, ranged from two to four and one-half days. The fourteenth person was digitalized in eighteen hours. The symptoms denoting full digitalization were the usual yellow vision, anorexia, nausea, abnormal sensation in the epigastrium (''pressure,'' ''flutter,'' ''uneasiness,'' ''fullness,'' ''excited feeling''), bradycardia, and lightheadedness. In one instance there were no subjective symptoms; only a marked bradycardia was noted. Electrocardiographic evidence of a digitalis effect was present in very few instances, and then only to a minor degree.

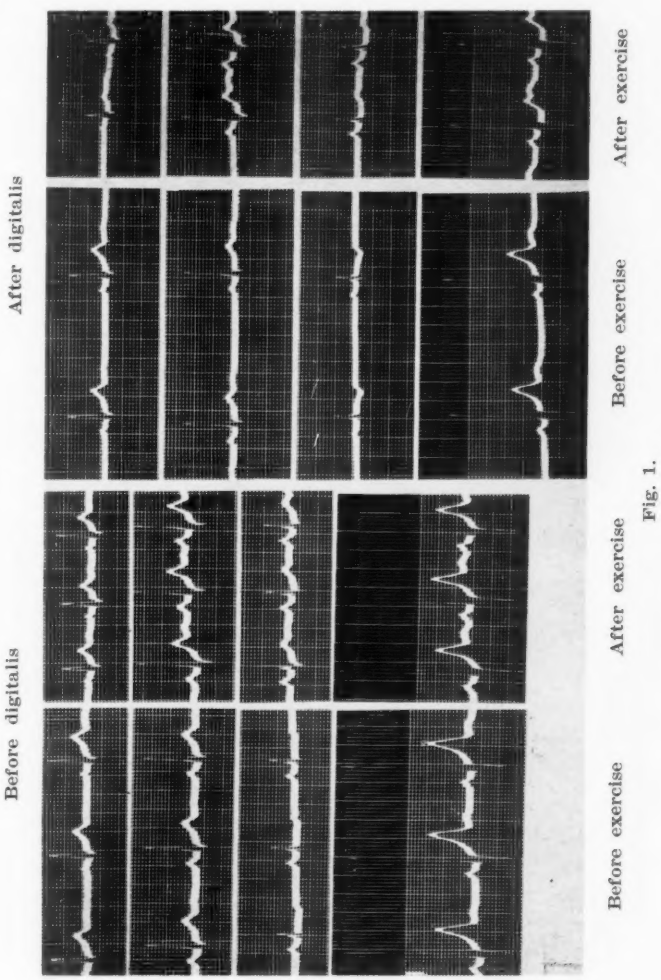

Fig. 1.

RESULTS

The outstanding change following exercise, after digitalization, was the general depression of the S-T junction. This, contrasted with the absence of such depression after exercise in the undigitalized subjects, is well illustrated in Table I. Indeed, in four subjects the deviation

of the S-T junction was greater than 1 mm. below the isoelectric line, which is generally accepted as distinctly abnormal.[2] Such changes are pictured in Figs. 1 and 2. This degree of depression of the S-T junction

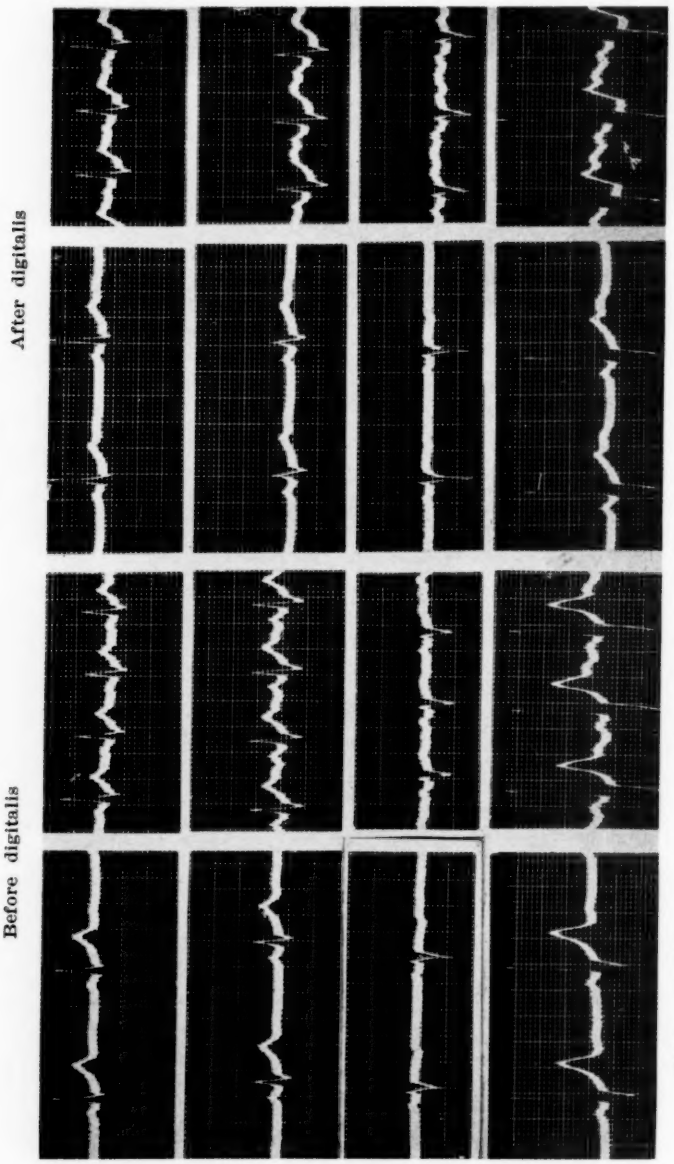

Fig. 2.

was never encountered in the undigitalized subjects. The changes may be compared with those which occur in a patient with coronary artery sclerosis before and during an attack of angina pectoris (Fig. 3).

After digitalization, exercise did not cause upright T waves to become inverted, but in four subjects an upright T wave became diphasic. Be-

fore digitalization, exercise had had a different effect. It caused an increase in the amplitude of the T waves in three of the subjects, and slight flattening in the fourth. In five subjects digitalization caused an upright T_3 to become diphasic, and after exercise the diphasic waves became completely inverted. Before these subjects were digitalized, exercise had caused slight flattening of T_3 in three instances, no change in one instance, and an actual increase in amplitude in the remaining case. Similarly, in one subject, records taken before exercise, both before and after digitalization, showed a diphasic T_3; before digitalization exercise caused the T wave to become upright, whereas after digitalization the diphasic wave developed a greater negative component.

A. *B.*

Fig. 3.—*A.* Patient at rest, without pain. *B.* Patient during attack of angina pectoris.

In two subjects exercise after the administration of digitalis was followed by relatively long periods of sinus arrest. In one record the R-R interval was 0.64 second, and the period of sinus arrest lasted 1.4 seconds; in the other the R-R interval was 0.72 second, and the period of asystole was 1.24 seconds. In the latter case P_3 became markedly inverted, although it had remained upright in the control.

COMMENT

It has been known for some time that electrocardiographic changes are associated with some attacks of angina pectoris. Feil and Siegel,[3] Parkinson and Bedford,[4] and Hall[5] have shown that with induced

attacks of pain there are depression of the S-T junction and diminution in the amplitude or inversion of the T waves in one or more leads. Wood and Wolferth[6] observed the same changes with both spontaneous and induced attacks. These facts have been put to clinical use in the diagnosis of angina pectoris. In a doubtful case an electrocardiogram is taken and the patient then exercises until pain is induced. An electrocardiogram is taken immediately to ascertain what changes have appeared. It is of great importance, therefore, that no factor other than the state of coronary flow affect the work electrocardiogram. We have shown that digitalization will produce, in a certain proportion of normal persons who experienced no pain, changes in the S-T junction and the T wave of the work electrocardiogram that resemble those in records taken during spontaneous or induced attacks of angina pectoris. Therefore, a check should be made in all cases concerning digitalis administration.

The question arises as to why digitalis causes such changes. The effect of this drug on the coronary arteries is still not known. Work on arterial strips, heart-lung preparations, and intact animals has yielded very different results. Gilbert and Fenn[7] found that digitalis bodies may exert a vasoconstrictor action; Essex, Herrick, and Visscher[8] observed no effect on the mean coronary flow; and Ginsberg, Stoland, and Siler[9] found a constrictor effect which they considered inconsequential. There is agreement, however, on the changes that occur in the electrocardiogram following anoxemia. Rothschild and Kissin[10] observed S-T deviation in both normal subjects and (particularly) people with angina pectoris during induced general anoxemia. Katz, Hamburger, and Schutz[11] observed flattening of T, occasional inversion of T in Lead III, and a downward shift of the S-T segment in normal subjects during generalized anoxemia. Levy, Barach, and Bruenn[12] reported slight flattening of T waves and a little depression of the S-T segments in normal subjects who breathed a low-oxygen mixture; in patients who had heart disease with cardiac pain, the anoxemia was associated with a change in amplitude, and occasionally in direction, of the T wave, and appreciable depression of the S-T segments. These changes caused by generalized anoxemia, particularly in patients with an impaired coronary circulation, are similar to those which occur in digitalized normal persons after exercise. It seems possible, then, that the oxygen supply to the heart during exercise is less after digitalization than in the undigitalized state.

SUMMARY

1. Exercise electrocardiograms were made of fourteen normal persons before and after digitalization.

2. When the subjects were digitalized, exercise caused a general depression of the S-T junction which in four instances was distinctly abnormal. Changes in T waves and rhythm also occurred.

3. It is therefore imperative that the digitalis effect on work electrocardiograms be not confused with work electrocardiograms which show the result of myocardial ischemia due to coronary artery disease.

REFERENCES

1. Zwillinger, L.: Die Digitaliseinwirkung auf das Arbeits-Elektrokardiogramm, Med. Klin. **30**: 977, 1935.
2. Feil, H.: The Chest Lead Electrocardiogram in Chronic Cardiac Anoxemia, Am. Assoc. Adv. Sc., Publication No. 13: 163, 1940.
3. Feil, H., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, Am. J. M. Sc. **175**: 255, 1928.
4. Parkinson, J., and Bedford, D. E.: Electrocardiographic Changes During Brief Attacks of Angina Pectoris; Their Bearing on the Origin of Anginal Pain, Lancet **1**: 15, 1931.
5. Hall, D.: Electrocardiograms of Two Patients During Attacks of Angina Pectoris, Lancet **1**: 1254, 1932.
6. Wood, F. C., and Wolferth, C. C.: Angina Pectoris, Arch. Int. Med. **47**: 339, 1931.
7. Gilbert, N. C., and Fenn, G. K.: Effect of Digitalis on the Coronary Flow, Arch. Int. Med. **50**: 668, 1932.
8. Essex, H. E., Herrick, J. F., and Visscher, M. B.: Influence of Certain Glucosides of Digitalis Lanata on the Coronary Blood Flow and Blood Pressure in the Trained Dog, AM. HEART J. **16**: 143, 1938.
9. Ginsberg, A. M., Stoland, O. O., and Siler, K. A.: Studies on Coronary Circulation. VI. The Effect of Some Members of the Digitalis Group on the Coronary Circulation, AM. HEART J. **16**: 663, 1938.
10. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, AM. HEART J. **8**: 745, 1933.
11. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris, AM. HEART J. **9**: 771, 1934.
12. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, AM. HEART J. **15**: 187, 1928.

MYOCARDIAL NECROSIS IN DIPHTHERIA

With a General Review of the Lesions of the Myocardium in Diphtheria

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DEATH of diphtheria patients from circulatory failure is a well-known and frequent occurrence, but the cause of the circulatory failure has been variously explained by different writers. Certain authors regard the cause as extracardiac. Romberg, et al.,[1] found that mechanical expression of blood from the splanchnic veins or compression of the aorta restored the heart's action in rabbits poisoned with diphtheria toxin, and considered that the heart failure was due not to myocardial damage but to a fall of blood pressure which they believed to be the result of poisoning or paralysis of the vasomotor center in the brain. Brodie,[2] experimenting with cats, thought that the cardiac death was caused by failure or relaxation of the blood vessels and the consequent fall in blood pressure, and Friedmann[3] regarded the diphtheria toxin as a specific poison for the blood vessels or the peripheral vasomotor nerves. MacCallum,[4] by artificially increasing the blood pressure in the aorta and by perfusing isolated hearts, found that the hearts from diphtheria-poisoned dogs could be made to continue or resume beating for hours by such means after circulatory collapse, or even death, had occurred. Thus it is generally conceded that circulatory failure in diphtheria may be a result of vasomotor paralysis without demonstrable myocardial damage. This is particularly true in cases in which death from circulatory failure occurred in the acute stage of the disease.

Again, certain authors attribute the cardiac failure to peripheral nerve degeneration. Veronese[5] found degeneration of the vagus, the cardiac ganglion, and the sympathetics, and maintained that this was the cause of the heart failure. Vincent[6] also regarded the vagal injury as essential. Thomas and Hibbard[7] concluded from their histologic studies of the nervous and myocardial lesions in diphtheria that the changes in the nerves were observed earlier and with greater constancy, and were therefore of greater importance than the myocardial degeneration, which they thought was secondary to vagal injury. On the other

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hand, Leyden,[8] Unruh,[9] Huguenin,[10] and Hochhaus[11] were unable to demonstrate any changes in the vagi and cardiac ganglia that they studied.

Abramow[12] found experimentally that large doses of diphtheria toxin caused suppression of the suprarenal secretion, and he ascribed the circulatory collapse in diphtheria to adrenal insufficiency.

That damage to the myocardium itself was also present was shown by MacCallum's[4] observation that the hearts of diphtheria-poisoned dogs did not continue to beat as long as the control hearts, were feeble in action, and showed a tendency to fibrillation, and by the electrocardiographic changes observed by a great many investigators (Nathanson,[13, 14] Begg,[15] Thompson, et al.,[16] Perry,[17] Boyle, et al.[18]) in diphtheria patients and in animals poisoned with diphtheria toxin. However, as regards the pathologic nature, the site, and the extent of the myocardial damage, and the significance of the myocardial lesions in relation to the cause of death, there exists much difference of opinion. MacCallum[19] and Donnerstag[20] found that the gross and microscopic changes in the heart were scarce and insignificant, and Loth[21] stated that the lesions were usually only cloudy swelling and focal fatty change and that a true myocarditis was only exceptionally demonstrable. The latter lesion has, however, been recognized by the majority of authors; Holt[22] considered toxic myocarditis more important than lesions of the cardiac nerves, especially in the late stage of the disease. Severe and extensive myocardial changes have been described by Councilman, et al.,[23] Price and Mackenzie,[24] Aviragnet, et al.,[25] and Warthin,[26] and Councilman, et al.,[23] stated that these changes were sufficient in themselves to cause cardiac insufficiency. Myocardial lesions have also been observed in experimental animals after injection of diphtheria toxin (Anitschkow,[27] Ma, Lieu, and Tung[28]). Flemming and Kennedy,[29] Löw,[30] Hume and Clegg,[31] Farr,[32] and Muir[33] described myocarditis involving the bundle of His, and Farr[32] even stated that the diphtheria toxin had a specific affinity for this structure. On the other hand, a lesion of the bundle was not regularly found by Aviragnet, et al.,[25] in cases in which there had been clinically demonstrable arrhythmias; Tanaka[34] found it only rarely in cases of fatal diphtheria; and Rohmer[35] stated that the diphtheria toxin showed no affinity for the bundle. Much controversy also exists as to the relative importance and frequency of the parenchymatous and interstitial lesions of the myocardium. Although the majority of authors regard a toxic parenchymatous myocarditis as the primary and important lesion, and the changes in the interstitial tissue as secondary and of a reparative nature, Leyden,[8] who found diffuse and overwhelming round cell infiltration in the interstitial tissue of the myocardium and only slight fatty change in the muscle fibers, attributed the cardiac failure to an interstitial myocarditis; Birch-Hirschfeld[36] even considered the interstitial changes as primary and the parenchymatous

changes as secondary; and Rabot and Philippe[37] stated that in their series of observations diphtheritic myocarditis was always of the interstitial type.

In view of the controversial state of the literature regarding the nature and extent of the myocardial lesion, and especially its significance in relation to the cause of cardiac failure, it is desirable to put on record the following case, in which the cardiac failure was adequately accounted for by extensive myocardial necrosis.

CASE REPORT

A Chinese girl, 17 years of age, was admitted with a history of serosanguinous discharge from the nose, severe sore throat, and inability to swallow and to speak for ten days. The onset of the illness was sudden and was followed by light cough. A week prior to admission she developed redness and swelling of the submaxillary region which persisted. There was no subjective feverishness. She had never been immunized against diphtheria.

Examination showed an undernourished, dehydrated, and critically ill patient. The voice was hoarse, but there was no respiratory distress. The skin was free from any kind of eruption. The conjunctivae were slightly congested. The nose was obstructed with serosanguinous discharge and crusts. The lips showed no cyanosis. A dirty necrotic membrane covered the whole throat from the soft palate to the posterior pharyngeal wall. It bled easily. The neck was not rigid. A number of enlarged and tender submaxillary lymph nodes were present on both sides. The lungs were normal. The heart was not enlarged. The heart sounds were normal, and there was no murmur. The cardiac rhythm was regular. The blood pressure was 82/52 mm. Hg. The abdomen was soft, and the liver and spleen were not palpable. The extremities and the reflexes were normal.

Examination of the blood showed 5,030,000 erythrocytes, 17.5 Gm. of hemoglobin, and 39,800 leucocytes, with 86 per cent polymorphonuclear neutrophilic leucocytes. The urine showed 2+ albumin, occasional erythrocytes and leucocytes, and many hyaline and granular casts. The stools were normal but contained ascaris ova. The throat smear showed diphtheria bacilli and spirochetes, but no fusiform bacilli. A culture from the throat swab showed diphtheria bacilli, and also *Streptococcus hemolyticus beta*. *Streptococcus hemolyticus beta*, but no diphtheria bacilli, were cultured from the nose swab. The Schick test was positive.

After admission, 30,000 units of diphtheria antitoxin were given intramuscularly. The dirty membrane in the throat gradually dropped off, leaving behind a raw surface with a big ulcerated area, about 1.5 cm. in diameter, involving the soft palate, pillars, fauces, and a part of the posterior pharyngeal wall. A 3 per cent solution of neoarsphenamine in glycerine was applied locally. The fluid and food intake was so poor that intravenous glucose infusions had to be given daily. Her general condition remained unimproved, and she died rather suddenly, but quietly, twenty-five minutes after the last infusion of 150 c.c. of 10 per cent glucose in normal saline, on the seventeenth day of the disease.

Post-Mortem Observations.—The entire pharyngeal wall was markedly congested and somewhat swollen. On the right lateral pharyngeal wall, and also, to a less extent, on the left pharyngeal wall, irregular, small ulcers, covered with purulent exudate, were found. The right tonsil was slightly enlarged, markedly congested, and superficially but extensively ulcerated. The left tonsil was not enlarged and showed no congestion or ulceration. The lymph nodules at the back of the tongue were very prominent. The submaxillary lymph nodes were swollen, and, on section, appeared juicy. The epiglottis and the arytenoepiglottic folds were edematous.

The mucosa of the larynx showed diffuse swelling and congestion, especially the vocal cords and the ventricular bands. The inner surface of the larynx was covered with a film or fibrinous exudate, mostly on the left, anterior side. The tracheal and bronchial mucosa also showed diffuse swelling and congestion. A film of fibrinous exudate was found over small areas of the trachea in its proximal portion just beneath the larynx, and a small amount of purulent exudate was present in the right bronchus just below the bifurcation of trachea. There was no actual diphtheritic membrane in the pharynx, larynx, or tracheobronchial system. Both lungs showed, on section, a few, small, scattered patches of early lobular consolidation. The tracheobronchial lymph nodes were not enlarged. Cultures taken from the pharynx, larynx, bronchus, and lung showed beta hemolytic streptococci, but no diphtheria bacilli.

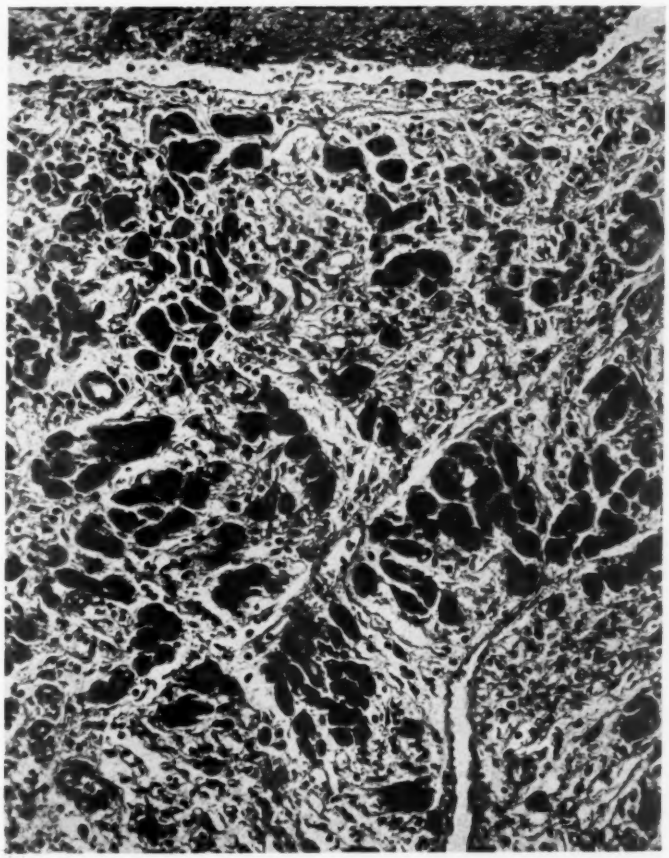

Fig. 1.—Extensive destruction of the myocardial fibers, proliferation of the connective tissue cells, cellular infiltration of the endocardium, and a mural thrombus (at the top of the picture). (×155.)

The heart was of normal weight (240 Gm.), but showed extreme dilatation of the left ventricle; numerous, fresh, mural thrombi were adherent to the endocardial surface of most of the wall of the left ventricle, and extended between the trabeculae carneae and papillary muscles. The left ventricular surface of the interventricular septum was smooth and free from mural thrombosis. The right auricle and ventricle were also markedly dilated, but showed no thrombi. The left auricle was normal. There were no valvular lesions. The aorta was smooth and elastic.

The liver showed marked central congestion, with a typical nutmeg appearance. The kidneys was markedly congested. Each pleural cavity contained about 1,500 c.c. of clear, straw-colored fluid, and the peritoneal cavity contained about 200 c.c. of similar fluid. Slight edema was present over the ankles and feet.

Grossly, the other organs were not striking.

Microscopically, sections of the larynx stained by the Gram-Weigert method showed numerous Gram-positive cocci in chains in the fibrinous pseudomembrane, but no diphtheria bacilli with Ponder's stain. The Giemsa stain revealed neither fusiform bacilli nor spirochetes in the ulcers of the pharyngeal wall and the tonsil, but numerous Gram-positive cocci in chains were present. Section of the cervical lymph node showed leucocytic infiltration in the marginal and medullary sinuses. Section of the lung showed small scattered patches where the alveoli were distended with leucocytes and fibrin and the bronchioles filled with purulent exudate. The spleen showed no follicular necrosis or leucocytic infiltration of the pulp. The kidneys showed marked degeneration of the convoluted tubules. The suprarenals were normal. The bone marrow of the femur was hyperplastic, with active granulopoiesis.

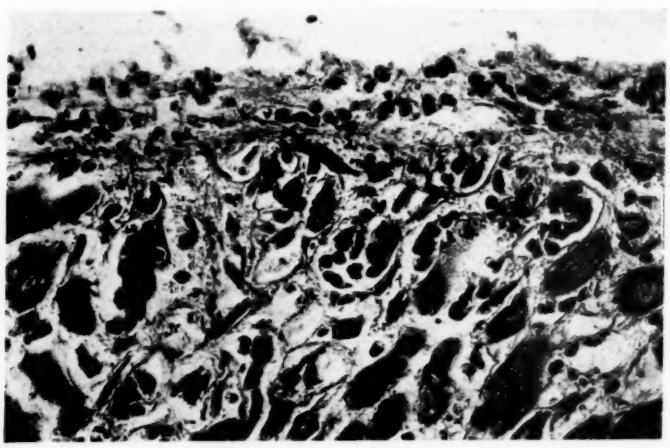

Fig. 2.—Two, necrotic, disintegrating, myocardial fibers (one in the right and the other in the left field of the picture), which are much more deeply stained (with eosin) than the relatively normal fibers, are distinctly granular in appearance and are infiltrated with polymorphonuclear leucocytes. In the middle of the picture, a histocyte can be seen occupying, together with several leucocytes, the space left by the disappearance of a myocardial fiber; above and a little to the left, a connective tissue cell (fibroblast) with a mitotic figure can be seen. In this picture there are many spindle-shaped fibroblasts (cut longitudinally) between the myocardial fibers (which are also cut longitudinally). Note also the leucocytic infiltration of the endocrardium. (×295.)

Section of the myocardium showed extensive destruction of the myocardial fibers (Fig. 1), although the sarcolemma sheaths were in most places still preserved (Fig. 3). Inside the sarcolemma sheaths, lumpy or granular acidophilic remains of the myocardial sarcoplasm were frequently found (Fig. 3). In the areas in which the muscle fibers had disappeared, there was proliferation of the connective tissue cells (Figs. 1, 2 and 3). Near the endocardium the lesions were more acute, and fresh necrosis of the myocardial fibers was observed. These necrotic fibers were more deeply stained with eosin than the relatively normal ones; they were distinctly granular in appearance and were infiltrated with polymorphonuclear leucocytes (Fig. 2). Histiocytes were also found among the leucocytes. The endocardium was heavily infiltrated with leucocytes (Fig. 2), and the endocarditis had caused fresh mural thrombosis. The thrombus presented the typical structure of corrugated laminae of platelets, interposed with masses of leucocytes and fibrin. No bacteria

were found in the myocardium or endocardium. Lesions of this nature and of varying degree were found in sections taken from various parts of the left ventricular walls; they were most marked in the apical and lateroposterior portion of the left ventricle, whereas sections from the portions of the interventricular septum in which the bundle of His lay, from the right ventricle, and from the auricles showed no lesions. Thus the extent of the lesions, as ascertained microscopically, corresponded well to the extent of the mural thrombosis which was found grossly. The liver showed marked central congestion and atrophy. The spleen showed marked congestion of the sinusoids. The kidneys also showed marked general injection of the blood capillaries.

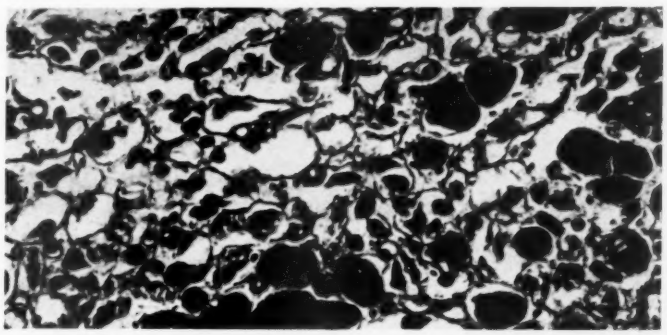

Fig. 3.—Showing disappearance of many myocardial fibers and persistence of the sarcolemma sheaths which describe the outlines of the lost myocardial fibers. Within the sarcolemma sheaths there can be seen irregular, lumpy, or granular, acidophilic remains of the myocardial sarcoplasm. The small cells with dark nuclei are fibroblasts cut transversely (the myocardial fibers in this picture are also cut transversely), and many of these cells are situated inside the sarcolemma sheaths. (×460.)

Anatomic Diagnosis.—History of pharyngeal diphtheria. Acute ulcerative pharyngitis and tonsillitis, diphtheritic laryngitis, and early lobular pneumonia, bilateral (*Streptococcus hemolyticus beta*); acute cervical lymphadenitis; acute myocardial necrosis, with fresh mural thrombosis of left ventricle; marked dilatation of heart; marked passive congestion of liver, spleen, and kidneys; slight ascites and hydrothorax; edema of ankles and feet; tubular degeneration of kidneys; hyperplasia of bone marrow.

DISCUSSION

There was very little doubt that the patient had a diphtheritic infection of the throat. The points in favor of such an impression were (1) the presence of a dirty necrotic membrane covering the whole throat, (2) the demonstration of diphtheria organisms in both the direct smear and the cultures, (3) the positive Schick test, (4) the response of the local lesion, in the form of disappearance of the membrane, after the injection of diphtheria antitoxin, and (5) the toxic manifestations in the absence of a marked febrile reaction, and the circulatory failure. The ulcerative pharyngitis and tonsillitis were, as shown by the results of culture and of direct staining of the sections, caused by the hemolytic streptococcus which is known to be the most frequent secondary invader in diphtheria infection. The film of fibrinous exudate in the larynx was evidently produced by the streptococcus, which is known to produce such exudates, and was present in the exudate in large numbers. If it

were a residual membrane due to diphtheria infection, Ponder's stain of the section and culture at autopsy should have demonstrated diphtheria bacilli.

The most striking feature of this case was the myocardial necrosis, which was evidently of a toxic nature, since no bacteria were found, and which caused the cardiac failure and fatal outcome. It means that, although the local infection was successfully controlled by antitoxin treatment, the myocardial damage already done by the diphtheria toxin was not affected by it. In the absence of obstruction of the upper respiratory tract and of extensive pneumonia, the marked central congestion and atrophy of the liver indicate that heart failure was present, and this also accounts for the congestion of the spleen and kidneys, the ascites, the hydrothorax, and the edema of the ankles and feet.

With diphtheria infection, myocardial necrosis or parenchymatous myocarditis has been described, although the circulatory failure is not seldom ascribed to vasomotor paralysis because actual myocardial damage is often morphologically not demonstrable. Since it is well known that, in the acute stage of diphtheria, death from circulatory failure is usually due to vasomotor paralysis, but that in the late stage or during convalescence it is usually caused by myocardial damage, lesions of the myocardium were to be expected in this case because the patient died on the seventeenth day of the disease.

However, a review of the literature (quoted in the appendix) reveals that the parenchymatous lesions most frequently found consist of fatty change, hyaline degeneration, and cloudy swelling, whereas true myocardial necrosis is comparatively rare, and that the lesions, except the fatty change, are usually focal and involve only portions of a myocardial fiber. Extensive, diffuse, myocardial necrosis such as was found in our case must, therefore, be considered unusual. The mural thrombosis observed in this case is also of infrequent occurrence, for relatively few authors among those reviewed (D'Espine and Mallet,[38] Councilman, et al.,[23] Thomas and Hibbard[7] and Aviragnet, et al.[25]) have referred to it. It was evidently secondary to the endocarditis, which, in turn, is secondary to myocardial necrosis, for exactly the same sequence of events occurs in myocardial infarction.

As to whether the extensiveness of the myocardial necrosis in our case was the result of a double infection with the beta streptococcus and diphtheria bacillus one cannot be certain, because, in most cases of diphtheria, there is, at autopsy, secondary streptococcus infection in the upper respiratory tract, and because such extensive myocardial necrosis is even more unusual in toxic streptococcal infections, e.g., scarlet fever.

The majority of authors consider the interstitial changes as a reaction to the parenchymatous lesion, and in our case the inflammatory cellular infiltration and connective tissue cell proliferation were indeed

TABLE I

AUTHOR	MYOCARDIAL LESIONS FOUND
Aviragnet, Lutembacher and Le Soudier[25]	Parenchyma: Atrophy, swelling, vacuolation, loss of striation, fragmentation, and a variety of nuclear changes (including karyorrhexis and karyolysis); no fatty change. Changes found throughout myocardium, but especially marked in region of the bundle. Endocarditis and thrombosis purely secondary and incidental. Interstitial tissue: Edema, leucocytes, mononuclears, and proliferation of fibroblasts.
Boyd[42]	Parenchyma: Acute toxic degeneration of muscle fibers, with swelling, granular appearance, loss of striations, hyaline degeneration, and necrosis. Only parts of a fiber involved. Interstitial tissue: Secondary inflammation, phagocytic and reparatory in nature.
Bouchut,[43] and Labadie-Lagrave[44]	Parenchyma: Fatty change frequent; waxy and granular degeneration rare.
Councilman, et al.[23]	Parenchyma: In early stage, fatty degeneration either general or focal, and of varying degree. Then swelling and breaking up into hyaline masses. Vacuolation; fragmentation. No bacteria found. Lesion of toxic nature. Thrombosis not an uncommon condition, and secondary to myocardial necrosis. Interstitial tissue: (1) Focal collections of plasma and lymphoid cells—independent of myocardial changes. (2) Proliferation of connective tissue cells (secondary to destruction of myocardial fibers. (Some cases of extensive fibrosis, so-called "fibrous myocarditis," of this etiology.)
D'Espine and Mallet[38]	Parenchyma: Mural thrombi on auricular and ventricular walls; parenchymatous myocarditis.
Donnerstag[20]	Parenchyma: Focal or diffuse fatty change; focal myolysis. Interstitial tissue: Interstitial inflammation sometimes found in late stage of myolysis; connective tissue cell proliferation, with scar formation, seen from beginning of third week of illness.
Farr[32]	Parenchyma: Focal waxy degeneration; focal round cell infiltration of sinoauricular node and bundle of His: widespread myocardial degeneration; fatty change; true myocarditis found once.
Flemming and Kennedy[29]	Parenchyma: S-A node and first portion of A-V bundle showed round cell infiltration, congested capillaries, a few large mononuclears, and some polymorphonuclears. Similar changes in auricular and ventricular myocardium.
Guttman[45]	Parenchyma: Cloudiness or turbidity. Interstitial tissue: Interstitial changes never found.
Hecht[46]	Parenchyma: Fatty change and cloudy swelling. Interstitial tissue: Round cell infiltration.
Heller[41]	Parenchyma: Granular degeneration commoner than fatty change; waxy degeneration also common, particularly in late stages; simple necrosis of portions of muscle fibers; perimysial tubes filled with detritus of dead muscle substance, leucocytes, and myogenic cells; evidence of muscle regeneration found. Interstitial tissue: Interstitial reparative reaction.
Hesse[47]	Parenchyma: Albuminous and fatty degeneration (more marked in early stage). Interstitial tissue: Interstitial myocarditis in late stage (due to changes in blood vessel walls); proliferation of connective tissue cells.
Hochhaus[11]	Interstitial tissue: Interstitial myocarditis similar to interstitial myositis of fauces, pharynx, and larynx.

TABLE I—CONT'D

AUTHOR	MYOCARDIAL LESIONS FOUND
Hoyne and Welford[48]	Parenchyma: Toxic parenchymatous degeneration; scattered hemorrhages in myo- and pericardium.
Huguenin[10]	Interstitial tissue: Connective tissue increased and infiltrated with small round cells. Blood vessels show endarteritis proliferans.
Hume and Clegg[31]	Parenchyma; Extreme diffuse fatty change. S-A node: congestion, hemorrhage, and lymphocytic infiltration. A-V node and bundle of His: capillary congestion.
Irwin[49]	Parenchyma: Focal or diffuse fatty degeneration; focal hyaline degeneration, or necrosis. Interstitial tissue: Endocarditis and pericarditis (usually due to streptococci) in less than 2% of cases.
Leyden[8]	Parenchyma: Slight fatty degeneration. Interstitial tissue: Diffuse and overwhelming round cell infiltration in connective tissue and around blood vessels (cardiac failure in diphtheria due to interstitial inflammation).
Loth[21]	Parenchyma: Mostly cloudy swelling and fatty change; acute myocarditis and myocardial necrosis exceptional.
Nuzum[39]	Interstitial tissue: Eosinophilic infiltration.
Oertel[50]	Parenchyma: Advanced fatty change in cases of long duration or great severity, with sudden death. Interstitial tissue: Hemorrhage and cellular infiltration.
Oheim[51, 52]	Parenchyma: Foci of waxy degeneration, myolysis, fatty change, calcification. Interstitial tissue: Edema; proliferation of connective tissue cells in areas of muscle destruction; perivascular leucocytic and lymphocytic infiltration.
Osler and McCrae[53]	Parenchyma: Fatty change in majority of cases; swelling and hyaline degeneration in advanced cases.
Rabot and Philippe[37]	Interstitial tissue: Myocarditis always of interstitial type, frequently in the form of focal round cell infiltration.
Romberg[54]	Parenchyma: Focal fatty, hyaline, and albuminous degeneration; transverse splitting (fragmentation).
Rosenbach[55]	Parenchyma: Intensive fatty, granular, and waxy degeneration.
Scagliosi[56]	Parenchyma: More or less diffuse fatty change; loss of striations; hyaline and homogeneous appearance, and intense eosinophilic staining; granular and waxy degeneration; muscle nuclei swollen and increased in number. (Changes only focal, and never involving the entire length of a fiber.) Site of predilection: trabeculae carneae and the zone immediately beneath the endocardium. Interstitial tissue: Marked injection of blood vessels; scattered hemorrhages; round cell infiltration around the degenerated muscle fibers (secondary or reactionary to parenchymatous change, because not found around normal myocardial fibers); blood vessels showed increase number of nuclei in intima, swelling of endothelial cells, hyalinization of media, and slight, small, round cell infiltration of adventitia. Fatty change of vessel wall not found.
Schamschin[57]	Interstitial tissue: Characteristic picture of interstitial myocarditis; slight fatty degeneration of walls of small arteries; lumen of vessel filled with lymphocytes and phagocytes loaded with fat.
Schemm[58]	Parenchyma: Fatty change, granular and hyaline degeneration; swelling; multiplication of nuclei.
Tanaka[34]	Parenchyma: Fatty change very common; fragmentation occasionally found. Interstitial tissue: Polymorphonuclear, eosinophilic, and mononuclear infiltration.

TABLE I—CONT'D

AUTHOR	MYOCARDIAL LESIONS FOUND
Thomas and Hibbard[7]	Parenchyma: Small foci showing loss of cross striations, swelling, paling, homogeneous staining (Zenker's degeneration), and vacuolation. Occasionally granular degeneration, atrophy of fibers and fragmentation, focal or extensive fatty change. Many fibers entirely destroyed. Lesion more marked just beneath endocardium; fresh thrombi adherent to myocardium. Interstitial tissue: Edema; infiltration with lymphocytes, large mononuclears, eosinophiles, leucocytes, plasma and epithelioid cells, in varying proportions.
Veronese[5]	Parenchyma: Degeneration. Interstitial tissue: Round cell infiltration.
Vincent[6]	Interstitial tissue: Increase of sarcolemma nuclei, capillary hemorrhages, and periarteritis.
Vulfius[40]	Interstitial tissue: Groups of eosinophiles in connective tissue.
Warthin[26]	Parenchyma: Toxic parenchymatous degeneration, most frequently of hyaline nature; necrosis associated frequently with fatty infiltration; cloudy swelling; or a simple necrosis. Muscle regeneration observed. The conducting as well as the contractile tissue may be affected. (Histologic picture depends on duration and stage of disease.) Interstitial tissue: Reparative inflammatory process; fibrosis.

limited to the areas where the myocardial fibers were undergoing necrosis or had disappeared. On the other hand, an independent interstitial inflammation, unassociated with a parenchymatous lesion, can certainly occur in diphtheria as well as in other acute infections (e.g., scarlet fever), and has been reported by many authors quoted in the appendix.

Review of the literature revealed two other points of interest: (1) that an eosinophilic myocarditis has been described by two authors (Nuzum,[39] Vulfius),[40] and (2) that three authors (Warthin,[26] Anitschkow,[27] Heller[41]) claimed to have observed regeneration of the myocardial fibers.

APPENDIX

(Review of the Lesions of the Myocardium in Diphtheria)

The nature, severity, and site of the lesions of the myocardium in diphtheria, as reported in the literature, vary a great deal, and, for comparative study, may be tabulated (Table I).

REFERENCES

1. Romberg, E., Pässler, H., Bruhns, C., and Müller, W.: Untersuchungen über die allgemeine Pathologie und Therapie der Kreislaufstörung bei acuten Infectionskrankheiten. I. Experimentelle Untersuchungen über die allgemeine Pathologie der Kreislaufstörung bei acuten Infectionskrankheiten, Deutsches. Arch. f. klin. Med. **64**: 652, 1899.
2. Brodie, T. G.: The Physiological Action of Diphtheria Toxin, Brit. M. J. **2**: 128, 1899.
3. Friedmann, U.: Pathogenese der diphterischen Kreislaufschwäche, Deutsches. med. Wchnschr. **58**: 1644, 1683, 1932.
4. MacCallum, W. G.: The Mechanism of the Circulatory Failure in Diphtheria, Am. J. Med. Sc. **147**: 37, 1914.
5. Veronese, F.: Die postdiphtherische Herzlähmung, eine anatomisch-pathologische und klinische Studie, Wien. klin. Wchnschr. **6**: 305, 327, 347, 367, 385, 401, 1893.

6. Vincent, H.: Sur les altérations du plexus cardiaque, dans la paralysie du coeur consécutive a la diphthérie, Arch. de méd. exper. et d'anat. pathol. **6:** 513, 1894.
7. Thomas, J. J., and Hibbard, C. M.: Heart Failure in Diphtheria, M. & S. Rep., Boston City Hosp. **11:** 204, 1900.
8. Leyden, E.: Über die Herzaffectionen bei der Diphtherie, Ztschr. f. klin. Med. **4:** 334, 1882.
9. Unruh: Über Myocarditis bei Diphtherie, Jahrb. f. Kinderh. **20:** 1, 1883.
10. Huguenin, P.: Contribution à l'étude de la myocardite infectieuse diphthérique, Rev. de méd. **8:** 790, 995, 1888.
11. Hochhaus: Über diphtherische Lähmungen, Virchows Arch. f. path Anat. **124:** 226, 1891.
12. Abramow, S.: Pathologisch-anatomische Studien über experimentelle Diphtherie-Intoxication und Diphtherie-Immunität, Ztschr. f. Immunitätsforsch. u. exper. Therap. **15:** 12, 1912.
13. Nathanson, M. H.: Observations on the Mechanism of Circulatory Failure in Diphtheria, Proc. Soc. Exper. Biol. & Med. **24:** 398, 1927.
14. Nathanson, M. H.: The Electrocardiogram in Diphtheria, Arch. Int. Med. **42:** 23, 1928.
15. Begg, N. D.: Diphtheritic Myocarditis, Lancet **1:** 857, 1937.
16. Thompson, W. P., Golden, S. E., and White, P. D.: The Heart Fifteen to Twenty Years After Severe Diphtheria, AM. HEART J. **13:** 534, 1937.
17. Perry, C. B.: Persistent Conduction Defects Following Diphtheria, Brit. Heart J. **1:** 117, 1939.
18. Boyle, R. W., McDonald, C. H., and De Groat, A. F.: The Effect of Diphtheria Toxin Upon the Heart, AM. HEART J. **18:** 201, 1939.
19. MacCallum, W. G.: Textbook of Pathology, ed. 6, Philadelphia and London, 1936, W. B. Saunders Co., p. 555-56.
20. Donnerstag: Herzveränderungen nach Diphtherie, Virchows Arch. f. path. Anat. **287:** 421, 1932.
21. Loth, M.: The Heart in Diphtheria, a Clinical and Pathological Study, Arch. Int. Med. **31:** 637, 1923.
22. Holt, L. E.: Diseases of Infancy and Childhood, New York, 1920, D. Appleton & Co., p. 835-1038.
23. Councilman, W. T., Mallory, F. B., and Pearce, R. M.: A Study of Bacteriology and Pathology of 220 Fatal Cases of Diphtheria, J. Boston Soc. M. Sc. **5:** 139, 1900.
24. Price and Mackenzie: Auricular Fbrillation and Heart Block, Heart **3:** 233, 1912.
25. Aviragnet, E. C., Lutembacher, R., and Le Soudier, M.: Le coeur dans la diphthérie, Arch. d. mal. du coeur. **11:** 241, 1918.
26. Warthin, A. S.: The Myocardial Lesions of Diphtheria, J. Infect. Dis. **35:** 32, 1924.
27. Anitschkow, N.: Über die Histogenese der Myokardveränderungen bei einigen Intoxikationen, Virchows. Arch. f. path. Anat. **211:** 193, 1913.
28. Ma, W. S., Lieu, V. T., and Tung, C. L.: Electrocardiographic and Anatomical Changes in Rabbits Poisoned by Diphtheria Toxin, Chinese M. J. (Supp. *3*), 574, 1940.
29. Flemming, G. B., and Kennedy, A. M.: A Case of Complete Heart Block in Diphtheria, With an Account of Postmortem Findings, Heart **2:** 77, 1910.
30. Löw, J.: Beiträge zur Pathologie des Reizleitungssystems, Ziegler's Beitr. **99:** 1, 1910.
31. Hume, W. E., and Clegg, S. J.: A Clinical and Pathological Study of the Heart in Diphtheria, Quart. J. Med. **8:** 1, 1914.
32. Farr, C. B.: The Significance of Arrhythmia in Infections of Childhood, With Special Reference to Diphtheria, Pennsylvania M. J. **23:** 633, 1920 (referred to by Loth).
33. Muir, Sir Robert: Textbook of Pathology, ed. 4, Baltimore, 1936, William Wood & Co., p. 337.
34. Tanaka, T.: Über die Veränderungen der Herzmuskulatur, vor allem des Atrioventrikular-Bündels bei Diphtherie, Virchows Arch. f. path. Anat. **207:** 115, 1912.
35. Rohmer, P.: Electrocardiographische und anatomische Untersuchungen über den Diphtherie-Herztod und dessen Beziehungen zum Reizleitungssystem, Ztschr. f. exper. Path. u. Therap. **11:** 426, 1912.
36. Birch-Hirschfeld: Jahrb. f. d. ges. Natur. u. Heilk., 1878-9, p. 26 (referred to by Warthin).

37. Rabot and Philippe: De la myocardite diphthéritique aiquë, Arch. de méd. exper. et d'anat. pathol. **3:** 646, 1891.
38. D'Espine and Mallet: Referred to by Loth.
39. Nuzum, F.: Eosinophylous myocarditis in diphtheria, J. A. M. A. **73:** 1925, 1919.
40. Vulfius: Vratch. Gaz., 1914 (referred to by Warthin).
41. Heller, A.: Über die Regeneration des Herzmuskels, Ziegler's Beitr. **57:** 223, 1914.
42. Boyd, W.: Textbook of Pathology, ed. 3, Philadelphia, 1938, Lea & Febiger.
43. Bouchut: Gazette des Hôpitaux, 1872, p. 937 (referred to by Scagliosi and Warthin).
44. Labadie-Lagrave: Des complications cardiaques du croup et de la diphthérie, Paris, 1873 (referred to by Scagliosi and Warthin).
45. Guttman, P.: Referred to by Scagliosi and Warthin.
46. Hecht, A. F.: Der Mechanismus der Herzaktion im Kindesalter, seine Physiologie und Pathologie, Ergebn. d. inn. Med. u. Kinderh. **2:** 324, 413, 1913.
47. Hesse, B.: Beiträge zur pathologische Anatomie des Diphtherieherzens, Jahrb. f. Kinderh. **36:** 19, 1894.
48. Hoyne, A., and Welford, N. T.: Diphtheria Myocarditis; Review of 496 Cases, J. Pediat. **5:** 642, 1934.
49. Irwin, R. L.: Essential Pathology Found in Diphtheria, Scarlet Fever, and Tuberculosis, With Special Reference to Involvement of Heart Based on Review of Necropsy Cases at Boston City Hospital for Past 40 Years, New England J. Med. **207:** 863, 1932.
50. Oertel: Experimentelle Untersuchungen über Diphtherie, Deutsches. Arch. f. klin. Med. **8:** 242, 1871.
51. Oheim, L.: Herzmuskelveränderungen bei Diphtherie, ihre zeitliche Aufeinanderfolge und topographische Verteilung, Ziegler's Beitr. **100:** 195, 1938.
52. Oheim, L.: Herzmuskelverkalkung bei Diphtherie, Ziegler's Beitr. **100:** 222, 1938.
53. Osler, W., and McCrae, T.: Principles and Practice of Medicine, New York and London, 1920, Appleton & Co.
54. Romberg, E.: Über die Erkrankunken des Herzmuskels bei Typhus abdominalis, Scharlach und Diphtherie, Deutsches. Arch. f. klin. Med. **48:** 369, 1891.
55. Rosenbach, J.: Über Myocarditis diphtheritica, Virchows Arch. f. path. Anat. **70:** 352, 1877.
56. Scagliosi, G.: Über die Veränderungen des Herzmuskels bei Diphtherie. Virchows Arch. f. path. Anat. **146:** 115, 1896.
57. Schamschin, W.: Beiträge zur Pathologie des Herzmuskels, Ziegler's Beitr. **18:** 47, 1895.
58. Schemm, G. C.: Über die Veränderungen des Herzmuskulatur bei Rachendiphtherie, Virchows Arch. f. path. Anat. **121:** 235, 1890.

Department of Clinical Reports

TUBERCULOUS PERIPHERAL ARTERITIS ASSOCIATED WITH TUBERCULOUS THROMBOPHLEBITIS IN THE LUNGS

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TUBERCULOUS arteritis of large peripheral arteries has been observed infrequently, whereas tuberculosis of the pulmonary vessels is probably present in every case of pulmonary tuberculosis. Search of the literature discloses, however, that tuberculous thrombophlebitis of the pulmonary vessels of such magnitude as to give rise to large emboli and metastatic foci of tuberculous arteritis in the large arteries of the periphery is sufficiently rare to justify recording this case.

The relationship between tuberculosis involving the vascular system and its generalized miliary dissemination was noted by Weigert,[1] in 1877. In the process of tuberculous cavitation, the vessels lying in the walls are encroached upon by the granulation tissue. As the adventitia and media are replaced by granulation tissue, the intima become thickened. When the walls of the cavity and artery have fused, the vessel may bulge, giving rise to the aneurysm of Rasmussen. Occasionally, rupture leads to severe hemoptysis; this, however, is usually prevented by intravascular thrombosis. Generalized miliary tuberculosis frequently results when a caseous process in a hilar lymph node erodes into the lumen of a pulmonary vein and discharges its infected contents into the blood stream.

In 1913, Haythorn[2] reported a case of tuberculous aneurysm involving the right common iliac artery. The patient was a man, aged 33 years. The clinical diagnosis was generalized miliary tuberculosis, chronic pulmonary and right-sided renal tuberculosis, tuberculous enteritis, and aortic aneurysm. At necropsy an aneurysm of the right common iliac artery was found; this aneurysm measured 7 cm. in breadth and 3 cm. in thickness. Its wall appeared to be continuous with the common iliac artery above, and with the internal iliac artery below. When the vessels were opened, the aneurysm was found to involve only the common iliac artery. The interior of the sac was almost filled with reddish-gray thrombotic material which appeared caseous. Histologic study showed

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that the outer wall of the sac was continuous with the adventitia of the common iliac artery below. Great numbers of acid-fast bacilli were demonstrated in the wall of the aneurysm, and in miliary lesions in the kidney, lungs, spleen, and liver. Haythorn[2] believed that the tuberculous process in this case originated in some adjacent focus, and the direct invasion of the adventitia so weakened the circular muscle fibers of the media that they ruptured. The continued pressure of the blood pouring through the opening divided the inner layers of the media from the outer medial layers and adventitia, resulting in a dissecting aneurysm. When the blood in the sac clotted, it became infected by the process in the adventitia. From this focus tubercle bacilli were disseminated throughout the blood stream. Haythorn[2] also classified the various kinds of tuberculous arterial lesions. He described them under four general types: (1) Miliary tuberculosis of the intima, (2) polypi of tuberculous tissue attached to the intima, (3) tuberculosis of the wall, involving all the layers, and (4) aneurysms, the walls of which were composed of tuberculous tissue.

In 1928, Malcolm[3] reported an aneurysm caused by tuberculosis in a man, aged 72 years. The patient had a right-sided, indirect, inguinal hernia for which he had worn a truss for many years. He died twenty-four days after a painful swelling appeared suddenly in the right thigh below Poupart's ligament. Autopsy disclosed generalized miliary tuberculosis, with a ruptured right femoral aneurysm caused by tuberculous arteritis. Hemorrhage was present about the right femoral artery. There was thrombosis of the femoral vein and its tributaries, as well as of the right femoral artery below the aneurysm. Microscopic examination revealed engorgement of the vessels of the adventitia. Extensive necrosis was present in all coats, with slight fibrous connective tissue proliferation. Giant cells were observed, but their character and location were not described. The acid-fast bacilli demonstrated in the media conformed to the size, shape, and staining reactions of the tubercle bacillus.

Brenner,[4] in 1935, indicated that tuberculous granulation tissue may extend along the lumen of a vessel for some distance before the wall becomes invaded. The extension of the thrombophlebitis to a large intrapulmonary vein results in a thrombus which is of sufficient size to give rise to embolism in peripheral arteries.

In 1939, Thieme and Maddock[5] described a case of "primary, tuberculous, peripheral vascular disease" in which no adjacent or other tuberculous processes were found, and no tubercle bacilli demonstrated.

At least twenty cases of tuberculosis of peripheral arteries, associated with aneurysm, have been reported. In five of these cases neighboring tuberculous processes were described. For instance, Thompson[6] reported related tuberculous lymph nodes. Brockman[7] and Ribbert[8] found the diseased artery in an area of tuberculous spondylitis.

The process of tuberculous aneurysm formation was described by Eppinger[9] as starting from embolic occlusion of one of the vasa vasorum, with resulting peri- and mesarteritis. When the elastica and adventitia are destroyed, the weakened vessel wall sacculates. Malcolm,[3] who found organisms only in the media, believed that his case was one of the kind described by Eppinger.[9] Le Noble[10] reported tuberculous nodules on the mitral valve, associated with peripheral arteritis and aneurysm.

CASE REPORT

A white woman, aged 21 years, was admitted to Cincinnati General Hospital on Sept. 13, 1939, because of marked dysphagia. The patient was in her sixth month of pregnancy. She had enjoyed good health until three months before admission, when she noticed the gradual onset of a moderately painful sore throat, followed by persistent hoarseness. The flow of saliva increased, and she frequently had nausea and vomiting. The act of swallowing became extremely painful, and frequently resulted in regurgitation of fluids into the nasopharynx.

There was no history of contact with tuberculosis. In 1937 and 1938 the patient had had attacks of transitory, severe, sore throat.

On physical examination the temperature by mouth was 103.4° F., the pulse rate, 128 per minute; the respiratory rate, 24 per minute; and the blood pressure, 100/60. The pale, poorly nourished patient had a roughened voice. She apparently preferred to allow profuse, thin, watery saliva to drool from the mouth rather than experience the pain of swallowing. The moderately swollen, red tonsils were covered with grayish-white membranes. An irregularly outlined area of ulceration extended from the tonsils over the anterior pillars and soft palate. The pale red, granular, ulcer bases were covered with patchy grayish-white exudate. The true and false vocal cords were somewhat swollen. The large, firm breasts presented pigmentation of the areolae and contained colostrum. The symmetrical chest expanded only moderately on respiration. The right middle lobe and both upper lobes of the lungs were normal to percussion and auscultation. The lower lobes were consolidated. The abdomen was enlarged by the gravid uterus, which extended above the umbilicus.

Throat cultures revealed the presence of hemolytic streptococci, colonies of *Staphylococcus aureus*, and many Gram-positive bacilli. The erythrocyte count was 3,460,000 per cubic millimeter. The leucocyte count was 7,800 per cubic millimeter, and remained low.

The condition of the patient became progressively worse, with elevation of the temperature, increasing dyspnea, cyanosis, and profuse sweating.

A 8:00 A.M. on the tenth hospital day there was a sudden onset of persistent, severe pain in the left foot. The foot promptly became cold. The patient soon complained of numbness and tingling in this foot. Reddish-blue, livid mottling appeared on the dorsum of the third and fourth toes. The coldness extended from the foot to midcalf. No pulsation could be felt in the dorsalis pedis, posterior tibial, popliteal, and femoral arteries of the left leg. All of the normal pulses were present in the warm right leg. The diagnosis of acute embolic occlusion of the left femoral artery was made, and passive vascular exercise was started seventeen hours after the recognized onset of acute arterial occlusion. The method consisted of applying, alternately, a positive pressure of 60 mm. of mercury and a negative pressure of 20 mm. of mercury twice a minute. The slow, rhythmic cycle was intended to overcome the intense arterial spasm set up by the arterial occlusion. As is usual when the patient is acutely ill, this treatment was somewhat tiresome.

Therefore, after two hours of treatment the foot was removed from the warm boot, wrapped in blankets, and allowed to rest for one hour. However, the respiratory rate rose to 68 per minute; cyanosis increased; and profuse sweating and a fall in blood pressure to 70/40 appeared. Meanwhile, the reddish-blue mottling of the foot had extended to the ankle. After twenty-six hours, passive vascular exercise was discontinued because of the critical condition of the patient and the progress of the arterial thrombosis in the proximal portion of the injured artery.

The patient died on the sixteenth hospital day, and an immediate cesarean section was done. An apparently normal, premature, male infant was delivered, but died fourteen days later of lobular pneumonia. Careful post-mortem examination of the infant did not reveal evidence of tuberculosis.

Necropsy on the mother showed generalized tuberculosis involving the lungs, liver, spleen, kidneys, suprarenals, intestine, breasts, placenta, tonsils, epiglottis, and vocal cords. Thromboarteritis and thrombophlebitis of the lungs were associated with recent pulmonary infarction and embolic occlusion of the external iliac artery.

The external iliac artery was distended throughout its entire extent, and its lumen was completely occluded by an adherent thrombus. The adventitia was dark blue, with irregularly mottled red areas. The clot in the lumen of the artery, in its most proximal and distal portion, had the character of a secondary red thrombus. The middle portion of the thrombus was white and firmly adherent.

Cross sections of the vessel were made at various levels; these were studied microscopically. In relation to the red thrombus, the vessel wall showed little evidence of disease. However, sections through the white thrombus disclosed a definitely laminated clot, with areas of caseous necrosis, associated with acute inflammatory changes throughout the arterial wall. The endothelium was completely destroyed. The intima was densely infiltrated with polymorphonuclear leucocytes and lymphocytes, many of which had undergone karyorrhexis and pyknosis. This process was often limited by the internal elastic lamella, but this was frequently fragmented by areas of caseous necrosis which extended into the media. Evident in the slightly congested adventitia were an extensive proliferative reaction of connective tissue and vascular endothelium and an infiltration of inflammatory cells, predominantly those belonging to the lymphoid and endothelial series. In occasional areas, however, the polymorphonuclear leucocytes were prominent. No foreign-body giant cells were observed in any of the sections of the artery. A small adjacent lymph node showed only rarefaction of the germinal centers, with proliferation of the reticulum. Acid-fast bacilli, which, in size, shape, and staining reactions, had the characteristics of tubercle bacilli, were demonstrated in the white thrombus, media, and adventitia, as well as in the generalized nodular lesions. No microorganisms were found in the nearby lymph node.

SUMMARY

Tuberculous arteritis of large peripheral arteries is frequently associated with aneurysm. In two of the twenty reported cases acid-fast bacilli were demonstrated.

A case of tuberculous arteritis as the result of embolism from tuberculous thrombophlebitis of pulmonary veins is reported. No aneurysm was present. The lumen of the artery was filled with a caseous white thrombus, and there were areas of inflammation and caseous necrosis in the intima and media and proliferation of connective tissue and vascular endothelium, with infiltration of lymphocytes and epithelioid

cells in the adventitia. No foreign-body giant cells were seen. Tubercle bacilli were demonstrated in the white thrombus, in the arterial wall, and in the lesions of generalized miliary tuberculosis.

REFERENCES

1. Weigert, C.: Ueber Venentuberkel und ihre Beziehungen zur tuberkulösen Blutinfection, Virchows Arch. f. path. Anat. **88**: 308, 1882.
2. Haythorn, S. R.: Tuberculous Aneurysm, Involving the Right Common Iliac Artery, J. A. M. A. **60**: 1414, 1913.
3. Malcolm, R. B.: Aneurysm Due to Tuberculosis With the Report of a Case of Tuberculous Aneurysm of the Right Femoral Artery, Canad. M. A. J. **19**: 33, 1928.
4. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. **56**: 1189, 1935.
5. Thieme, T., and Maddock, W. G.: Primary Tuberculous, Peripheral Vascular Disease, Surgery **6**: 604, 1939.
6. Thompson, W. P.: Tuberculous Aneurysm of Hepatic Artery, Bull. Johns Hopkins Hosp. **42**: 113, 1928.
7. Brockman, E. P.: Aneurysm of the Femoral Artery in a Patient With Pott's Disease of the Spine, Brit. J. Surg. **14**: 669, 1927.
8. Ribbert: Mitteilung über ein tuberkuloses Aneurysma der Aorta, Sitzungsb. d. Nied-rhein, Gesellsch. f. Nat. und Heilk. 24 Bonn, med. section, May 14, 1910.
9. Eppinger: Pathogenesis (Histogenesis and Aetiologie) der Aneurysmen, Arch. f. klin. Chir. **35**: Suppl. 156, 1887.
10. Le Noble, Pel.: Aneurisme de la portion initiale de l'aorte, Arch. d. mal. du coeur **15**: 677, 1922.

CORONARY ARTERY THROMBOSIS, WITH RECOVERY, IN A CASE OF THROMBOANGIITIS OBLITERANS

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IN 1879, von Winiwater[1] reported occlusion of the arteries of both lower extremities by a chronic proliferative process arising from the intima of the vessels. Microscopic sections of these vessels showed an inflammatory reaction in their walls. This lesion was called endarteritis obliterans. Thereafter, occasional reports appeared describing similar pathologic processes. Buerger[2] called attention to the thrombotic and inflammatory nature of the process, the involvement of veins as well as arteries, and the characteristic clinical phenomena of the disease which now bears his name. From a review of the literature, one is impressed with the fact that thromboangiitis obliterans is not a rare disease. Averbuck and Silbert[3] and Cohen and Barron[4] have noted that thromboangiitis obliterans is not restricted to the vessels of the extremities. The literature is rich in clinical, pathologic, and experimental data dealing with the various types of coronary artery thromboses. However, there is a paucity of reports concerning the occurrence of coronary thrombosis in cases of thromboangiitis obliterans.

CASE REPORT

A. S., a 40-year-old man, was first seen in September, 1935, when he was complaining of pain in the left large toe of one year's duration. During the preceding winter he noticed that he was much more sensitive to cold than he had been previously, and for eight months he had had an ulcer on the left large toe which did not respond to a variety of self-prescribed ointments. He slept poorly because of the burning pain. The patient admitted smoking thirty to forty cigarettes daily, and, for many years, he had eaten four to five slices of rye bread daily. The remainder of his history was noncontributory except for the fact that he had had gonorrhea when he was 19 years of age.

The blood pressure was 124/80. At the tip of the left large toe there was an open ulcer which measured 0.5 by 0.25 inch and had undermined edges and a necrotic base. The extremities were cold to the touch below the level of the lower one-third of the leg. There was moderate cyanosis of both lower extremities on dependency, with a cyanotic rubor of the left large toe. There was marked pallor on elevation. The dorsalis pedis and posterior tibial pulsations were absent. The pulsation of the popliteal vessels was easily palpated. The maximum oscillometric readings at the levels indicated are given in Table I. Roentgenologic examination of the lower extremities showed no evidence of calcification of the vessel walls.

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The patient was advised to stop smoking cigarettes and eating rye bread, was instructed concerning exercises and hygiene of his extremities, and was given two intravenous injections of typhoid vaccine. He had a rather severe reaction after each injection and refused to return for further therapy.

TABLE I

MAXIMUM OSCILLOMETRIC READINGS

LEVEL	RIGHT	LEFT
Thigh	4.5	5.0
Leg	3.0	3.0
Ankle	0.5	0.25
Foot	0	0

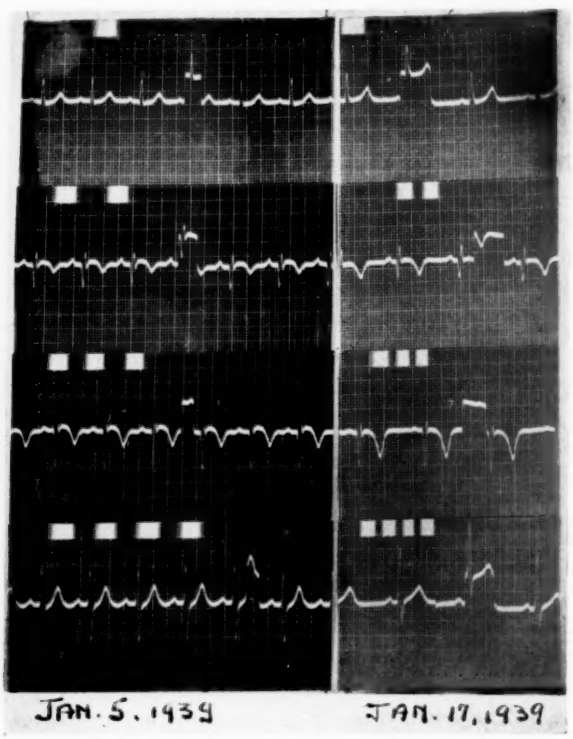

Fig. 1.—Electrocardiograms taken Jan. 5, 1939, and Jan. 17, 1939, showing elevation of R-T_2 and R-T_3, with inversion of T_2 and T_3. Lead IVF shows no change except that S_4 in the second electrocardiogram is not so deep as in the first.

The patient was not seen again until March, 1938, when he returned with an open ulcer on the plantar surface of the right foot; the ulcer had been present for three weeks. The interval history revealed the fact that the ulcer on the left large toe had healed, and the patient had been able to walk about ten blocks without discomfort. He stated that he felt so well that he had even begun to smoke cigarettes again. After he started to smoke, his claudication distance gradually grew shorter and shorter, so that, on his second admission, he was able to walk only one-half block before pain forced him to stop. At this time he had marked rubor on dependency, trophic changes in all of the toenails, and cadaveric pallor on elevation. There was an ulcer measuring about ½ by ¾ inch on the plantar surface of the right foot at

the head of the third metatarsal bone. Oscillometric studies revealed essentially the same readings as on the first examination. He received a course of typhoid H antigen injections. The ulcer healed in three months. While he was under observation, the patient did not smoke.

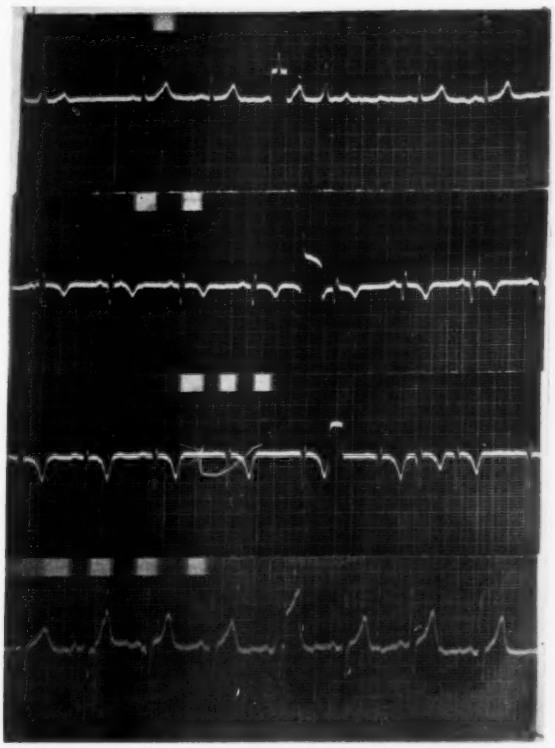

Fig. 2.—Electrocardiogram taken Jan. 30, 1939, showing ventricular premature contractions in Lead III.

The patient was not seen again until Jan. 2, 1939, when, after exertion incident to lifting and adjusting snowplows to trucks, he was seized with sudden, severe, precordial pain which radiated to the neck and jaw and down both arms. He complained of feeling nauseated, but he did not vomit. He rested for about one-half hour, and then completed his day's work. He went home and remained in bed for forty-eight hours. The pains were thought to be gas pains. He then returned to work and shoveled coal into a furnace. While doing this he was seized again with precordial distress which was more severe. He was nauseated but did not vomit. He began to perspire freely and felt weak. He had a fear of impending dissolution. He went home and was examined immediately. His expression was a mixture of fear and anxiety. He had circumoral pallor; his lips were cyanotic; and his respirations were rapid. His blood pressure was 90/70, and his temperature, 99.2° F. The heart tones were heard with difficulty. There was no friction rub. The pulse rate was 120 per minute. The edge of the liver was palpable 1.5 fingerbreadths below the costal margin; it was soft and tender. The spleen was not enlarged. No pulsation could be felt in the major vessels of the lower extremities. The nail beds were cyanotic. An electrocardiogram taken Jan. 6, 1940, revealed the T_2-T_3 type (Fig. 1) of changes which are typical of posterior wall infarction. The sedimentation rate

was rapid (17 mm. in one hour). The leucocyte count was 11,000, 78 per cent of which were polymorphonuclears, and his temperature rose to 101° F. His precordial distress subsided, and the temperature, sedimentation rate, and leucocyte count returned to normal. About twenty-seven days after the occlusion the pulse became somewhat irregular; this irregularity was caused by frequent ventricular premature contractions, as shown by an electrocardiogram (Fig. 2).

The patient made an uneventful recovery. A follow-up examination (June, 1940) revealed no further advance in the vascular process, either in the extremities or in the coronary vessels. He has given up smoking completely, and he is able to work eight hours daily at laborious tasks.

The protocol of a 44-year-old man who died from thromboangiitis obliterans of the left common iliac artery, with extension into the aorta as far as the left renal artery, was recorded by Perla.[5] An organized, canalized thrombus almost completely occluding the lumen of the left coronary artery 1.5 cm. from its aortic orifice was found. The pathologic process in this coronary artery resembled that in the diseased vessels of the extremities. Barron and Linenthal[6] observed coronary thrombosis in one of twenty-seven cases of thromboangiitis obliterans which they collected. These authors noted that the disease involves the walls of arteries, as well as veins, throughout the entire vascular system. Myocardial damage which Samuels and Feinberg[7] attributed to involvement of the coronary arteries by thromboangiitis obliterans was noted in five of their fifty cases. Allen and Willius[8] observed clinical evidence of disease of the coronary arteries in seven of a series of 225 unselected cases of thromboangiitis obliterans. Six patients had definite electrocardiographic evidence of involvement of the coronary arteries. The remaining electrocardiogram was normal, in spite of the fact that the patient was a 47-year-old man who complained of choking sensations, severe pain across the anterior, lower part of the chest and down both arms, and dyspnea on exertion.

Fatherree and Hines[9] reviewed forty cases from the literature. The diagnostic criteria for thromboangiitis obliterans were adequate and the cause of death was established by necropsy. In three of the nine cases in which death occurred after operation, and, in twenty-three in which death did not follow operation, occlusive arterial disease in locations other than the extremities played a dominant role as a cause of death. Ten of the twenty-three nonpostoperative deaths were caused by coronary thrombosis. An analysis of the data led these authors to the conclusion that by far the most common extraperipheral cause of death in cases of Buerger's disease is coronary thrombosis. However, Allen and Willius[8] observed that the incidence of coronary artery disease in cases of known thromboangiitis obliterans was no greater than in a control group.

A prolonged discussion of Buerger's disease or coronary artery thrombosis is not necessary here. Speculation as to the relationship of the

attack of coronary artery occlusion to the present conception of the universal nature of the vascular involvement in Buerger's disease is of interest. The occurrence of coronary artery thrombosis after unusual effort has been discussed by Boas.[10] The idea that thromboangiitis obliterans is a generalized vascular disease, rather than a disease involving only the vessels of the lower extremities, has been accepted.

SUMMARY

A case of coronary artery thrombosis, with recovery, in a 40-year-old man with known thromboangiitis obliterans is reported.

REFERENCES

1. Von Winiwater, F.: Über eine eigentümliche form von Endarteritis und Endophlebitis mit Gangrän des Fusses, Arch. f. klin. Chir. **23**: 202, 1879.
2. Buerger, L.: Thromboangiitis Obliterans. A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene, Am. J. M. Sc. **13**: 567, 1908.
3. Averbuck, S. H., and Silbert, S.: Thromboangiitis Obliterans. IX. The Cause of Death, Arch. Int. Med. **54**: 436, 1934.
4. Cohen, S. S., and Barron, M. E.: Thromboangiitis Obliterans With Special Reference to Its Abdominal Manifestations, New England J. Med. **214**: 1275, 1936.
5. Perla, D.: An Analysis of 41 Cases of Thromboangiitis Obliterans, Surg, Gynec. & Obst. **41**: 21, 1925.
6. Barron, M. E., and Linenthal, H.: Thromboangiitis Obliterans, General Distribution of the Disease, Arch. Surg. **19**: 735, 1929.
7. Samuels, S. S., and Feinberg, S. C.: The Heart in Thromboangiitis Obliterans, Am. Heart J. **6**: 255, 1930.
8. Allen, E. V., and Willius, F. A.: Disease of the Coronary Arteries Associated With Thromboangiitis Obliterans of the Extremities, Ann. Int. Med. **3**: 35, 1929.
9. Fatherree, T. J., and Hines, E. A.: Vascular Clinics. IV. Fatal Complications of Thromboangiitis Obliterans. A Clinical Study, Proc. Staff Meet., Mayo Clin. **13**: 842, 1938.
10. Boas, E.: Angina Pectoris and Cardiac Infarction From Trauma or Unusual Effort, J. A. M. A. **112**: 1887, 1939.

Department of Reviews and Abstracts

Selected Abstracts

Katz, L. N., Jochim, K., Lindner, E., and Landowne, M.: The Effect of Varying Resistance-Load and Input-Load on the Energetics of the Surviving Mammalian Heart. Am. J. Physiol. **134**: 636, 1941.

A method is described for obtaining a true mixed coronary venous blood sample in the heart-lung or isolated heart preparation of the dog, and for calculating the true oxygen consumption of the heart.

Measurements of oxygen consumption and work of the heart preparation indicate that the increase in oxygen consumption consequent upon an increase in work depends not only upon the magnitude of the work increase, but also on whether the augmented work is produced by raising (1) the venous return or (2) the peripheral resistance. In the former case the increase in oxygen consumption is proportionally less than in the latter, so that a given amount of work is done more efficiently with a large venous return and a low peripheral resistance than the same amount of work done with a low venous return and a high peripheral resistance.

AUTHORS.

Weltz, G. A.: Effect of Respiration on Filling and Rate of Heart. Arch. f. Kreislaufforsch. **8**: 1, 1941.

By means of roentgenkymography, electrocardiograms, pneumotachygrams and plethysmography of the limb on human and on animal subjects, an investigation of effects of respiration were made. It was found that there is a respiratory fluctuation in the venous return to the heart, which normally consisted of an increase in inspiration. This is associated with a reflex pulse acceleration. Under certain abnormal circumstances, such as artificial respiration, the inspiratory increase in venous flow to the heart is decreased and with it there is a cardiac slowing instead of an acceleration in inspiration.

KATZ.

Starr, I.: Clinical Studies With the Ballistocardiograph: In Congestive Failure, on Digitalis Action, on Changes in Ballistic Form, and in Certain Acute Experiments. Am. J. M. Sc. **202**: 469, 1941.

This presentation is designed to demonstrate the utility of the ballistocardiogram as an instrument of the diagnosis of cardiac and circulatory abnormality and for the solution of certain clinical problems. Records are presented indicating changes in the circulation in congestive heart failure and on recovery from it, during digitalis action, and in various arrhythmias in one patient.

The method is suited especially for acute clinical experiments. The examples cited include ballistocardiograms from a case of traumatic arteriovenous communication before and during occlusion of the communication and similar records from a patient

with angina pectoris in whom pain was produced by the injection of fluid down a drainage tube into the common bile duct.

Changes in the form of the ballistic record provide evidence of cardiac dysfunction of a type not obtainable by other methods. The examples cited were obtained from three patients in whom the abnormality followed operative procedures and disappeared as strength was regained.

AUTHOR.

Baer, S., and Isard, H. J.: A Correlation of the Velocity of Blood Flow and the Basal Metabolic Rate in Various Metabolic Disorders. Arch. Int. Med. **67**: 939, 1941.

An attempt has been made to determine what correlation, if any, existed between the basal metabolic rate and the velocity of blood flow. Basal metabolic rates and circulation times were determined in 187 patients. After the injection of 4 c.c. of a 20 per cent solution of calcium gluconate intravenously, the circulation time was measured from the instant the injection was begun until the patient noticed a sensation of heat in the oropharynx.

In 227 trials, the normal arm-to-tongue time varied from nine to sixteen seconds, with an average of 12.1 seconds. In twenty-four patients with hyperthyroidism, the average circulation time was 8.9 seconds, and in hypothyroidism the circulation time was usually prolonged beyond sixteen seconds. Thus, the velocity of blood flow is increased in hyperthyroidism and decreased in hypothyroidism.

In cases of polyglandular dystrophy however, or those patients with menopausal syndromes and hypertension, the calcium gluconate circulation time bears no relation whatsoever to the B.M.R. In children, irrespective of the basal metabolic rate, the velocity of blood flow is increased.

The authors feel that the determination of the velocity of blood flow may be of some help in the diagnosis of thyroid gland disturbances. A basal metabolic rate of plus 20 or above and an arm-to-tongue circulation time of ten seconds or below are strongly suggestive of active hyperthyroidism.

AUTHOR.

Moe, Gordon K., Harris, A. S., and Wiggers, C. J.: Analysis of the Initiation of Fibrillation by Electrographic Studies. Am. J. Physiol. **143**: 473, 1941.

The mechanism by which ventricular fibrillation develops as a result of a strong, brief D. C. shock delivered during the vulnerable period of the ventricular cycle was studied electrographically. Three pairs of contiguous electrodes operating on the principle of Garten differential electrodes were variously oriented on the ventricular surface with respect to the site of stimulation in different tests on the same heart. Since the ventricles were repeatedly revived by the countershock method of Hooker, the ventricular surface was sampled reasonably well by changing the placement of electrodes.

The following results and conclusions are discussed.

A moderately strong, brief shock applied considerably before the T wave of an electrogram recorded at, or near, the point of stimulation causes one response shortly after the T wave. Tests are presented which indicate that the response is probably not due to an actual systolic excitation but to the creation in tissue of a decrementing polarization potential which is sufficient in duration and intensity to excite early in the next relatively refractory phase. In this way the response of the ventricle to a systolic shock can be harmonized with the existence of a refractory state in muscle fractions. It also explains why the latency of responses at definite points on the cardiac surface remains constant for shocks applied at any moment of diastole, but

increases linearly as they are applied more and more in advance of the T wave of a local electrogram. No evidence has been found in the dog's heart that changes in conduction are involved in such increasing latency; the interpunctal differences between excitation lines remain the same, regardless of when the stimulus is introduced.

A very strong shock applied to a discrete mass of ventricular muscle during the Q-T interval of an adjacent electrogram evokes a series of deflections in all electrograms led from the cardiac surface. This may be followed by a pause and resumption of normal rhythm or by fibrillation. When the latter occurs, it develops in the nearest surface lead slightly before it does in the others.

The series of discrete deflections recur at progressively decreasing intervals in the most proximal lead, and the excitation times more distant in relation to proximal points increase progressively during the series of responses.

The order of excitation on the surface and interior of the ventricle during the second, third, and fourth responses and the existence of a period between beats when no area is excited do not support the view that the initial beats are due to re-entry of impulses. On the contrary, the concentric arrangement of isochrons calculated from actual records strongly suggests repetitive emission of several impulses from the stimulated area, temporarily made automatic by the shock.

Deflections similar in form and sequence in near and far areas of the heart could be caused artificially by applying a series of weak threshold break induction shocks at slightly diminishing intervals. If given in proper sequence, these also cause fibrillation.

The conclusion is drawn that the re-entry of impulses, with which fibrillation following localized application of a strong, brief D. C. shock starts, is due to the progressive decrease in refractory period combined with a progressive increase in conduction time. This starts in regions near the site of stimulation and occurs as a result of the repetitive accelerating discharges rather than as an effect of the current per se. In short, while repetitive discharges from a center or centers are not required to sustain fibrillation, they are essential to its initiation after a strong electrical shock.

AUTHORS.

Wiggers, C. J.: The Mechanisms of Peripheral Circulatory Failure. Ann. Int. Med. **15**: 178, 1941,

In this brief discussion the author reviews the fundamental factors involved in peripheral circulatory failure. He discusses the four mechanisms which have been suggested and can be supported by experimental evidence. They are (1) primary arteriolar dilatation, (2) primary arteriolar constriction, (3) primary atony and dilatation of capillaries and (4) primary failure of some venopressor mechanism.

It is obvious that this problem is still worthy of investigation and that the answer has not yet been found to the many questions involved.

MCCULLOCH.

Fouts, P. J., Corcoran, A. C., and Page, I. H.: Observations on the Clinical and Functional Course of Nephrotoxic Nephritis in Dogs. Am. J. M. Sc. **201**: 313, 1941.

Nephrotoxic nephritis due to injection of relative organ-specific nephrotoxic sera in dogs is at its onset associated with increased renal blood flow and decreased efficiency of glomerular filtration.

The decrease of glomerular efficiency is apparently due to thickening of the glomerular basement membrane. This functional alteration persists during the course

of active nephritis. Its presence is indicated by an increase in the ratio of phenol red to inulin clearance.

The hematuria which is observed at the onset of nephrotoxic nephritis in the dog and during the persistence of severe chronic nephritis is apparently not related to hemolytic or anaphylactic reactions which may follow the injection of sera.

Although the acute anemia which followed injection of nephrotoxic sera in dogs is due to hemolytic factors present in the sera, the course of the anemia subsequent to the development of nephritis suggests that depression of bone marrow activity is present during the persistence of severe renal disease.

AUTHORS.

Boyd, L. J., and Scherf, D.: The Electrocardiogram in Acute Emetine Intoxication. J. Pharmacol. & Exper. Therap. **71**: 362, 1941.

The alterations of the electrocardiogram after the intravenous administration of emetine hydrochloride were studied in dogs and cats.

Disturbance of intraventricular conduction is the most common change observed under these circumstances. Bradycardia and prolongation of atrioventricular conduction time develop regularly, but they are not pronounced.

If the intravenous dose does not exceed 37 mg. in dogs weighing 5 to 9 kg., the electrocardiographic alterations gradually disappear within forty-five minutes. Cardiac dilatation, especially involving the right ventricle, the development of which is simultaneous with the ventricular conduction disturbances, also vanishes within the same period.

The action of emetine is cumulative since much more pronounced effects result from the second or third injection of an equal amount of the drug although the normal electrocardiogram has been restored.

The most common arrhythmias to develop are auricular extrasystoles and auricular tachycardias. Alternation of the ventricular complexes is frequently observed during the tachycardia. Advanced stages of intoxication are required for the production of ventricular extrasystoles. Heart block with dropped beats was encountered only in cats.

AUTHORS.

Campbell, H. E.: The Statistical Method. A Vital Tool in Clinical Medicine. Surgery **9**: 825, 1941.

Clinicians have almost entirely neglected criteria of statistical analysis in their scientific writings. The many contradictory teachings and controversial practices originate in part in this neglect of well-recognized statistical procedure.

We have described in detail the derivation and application of the simpler formulas as they relate to percentages. With a little thought every doctor can master this technique and apply it in a very few minutes to medical papers which utilize percentages in their conclusions.

As presented now, most case series are too brief for sound conclusions. Publication should be withheld until longer series are amassed. A standard classification in such diseases as are now the center of controversy would enable short series to be combined and allow reliable conclusions to emerge.

Medical students should receive formal education in statistical procedure. Medical editors should demand of medical authors that their figures and data be statistically sound.

AUTHOR.

Book Reviews

SYNOPSIS OF DISEASES OF THE HEART AND ARTERIES: By George R. Herrmann, M.D., Professor of Medicine, University of Texas. The C. V. Mosby Co., St. Louis, 1941, Ed. 2, 468 pages, 91 illustrations, $5.00.

Those not familiar with the first edition of this book might easily be misled by the term "Synopsis" into expecting a small brochure containing a very brief tabular summary of the most important facts relating to cardiac and arterial disease. The book is small in format, and might easily fit in the pocket of an overcoat, but it contains 450 pages of text, which is equivalent to 300 or more pages of the standard octavo volumes. It is in fact a synopsis, but a very full and extensive one.

To those engaged in study or practice in this field of medicine the author is well known for his many contributions to its advancement. To all such it is unnecessary to say that he speaks with the authority born of long experience as an investigator, teacher, professor of medicine, and consultant in active practice. This experience has fitted him admirably to survey the broad field of cardiovascular diseases and sift out of the formidable mass of material that which is really important and useful for advanced students and practitioners. The first edition of the book seemed to this reviewer the best summary of the subject that had ever appeared in English, and the present (second) edition fully sustains the splendid reputation of its predecessor.

To read the volume through from beginning to end is to discover a fault that is probably inevitable in a book of this type, intended primarily for reference. There is a certain amount of repetition in the discussion of related topics which would not be apparent in reading a single section or chapter. The only other adverse criticism that I would offer is that more space is devoted to chronic cardiac valvular disease (with separate chapters on aortic, mitral, and tricuspid valvular disease) than seems warranted in view of the current belief that etiology and functional condition are vastly more important than structural lesions.

There is no important aspect of cardiovascular disease that is omitted. The discussions are clear, comprehensive, authoritative, and up to date. If the author differs from other authorities in certain respects, it is almost invariably upon matters that are still unsettled, and his opinion may well be the correct one.

The book is cordially commended to all who desire a brief, authoritative discussion of the diagnosis and treatment of cardiovascular diseases.

H. M. MARVIN.

YOUR HEART: By Joseph M. Stein, M.D. Alliance Book Corporation, New York, 1941, 240 pages, $2.75.

This book is designed for the laity, and presents much worth-while information concerning the heart, its function, and the diseases to which it is subject. It is predominantly optimistic in its approach, and does not present the material in such a manner as to frighten the cardiac patient, but offers encouragement to those who follow the regime outlined. The suggestions on the mode of life, the mental attitude, occupations, and avocations, and the general regimen to be followed are

helpful, but the book in no way attempts to prescribe for the patient. The endeavor to create popular appeal has led the author to a verbose and flowery presentation of some features in the early chapters, but this style does not persist throughout.

The implications which are made as to the effect of diseases of the teeth and tonsils on heart disease do not seem to be justified, and the relationship between angina pectoris and coronary artery disease is probably more close than is implied in the book. The results of surgical procedures on the heart do not yet justify the author's optimistic reports, especially in respect to those designed to remedy the effects of coronary occlusion. The best and most important features are the advice and encouragement offered to those patients with early or mild cardiac disease.

W. M. FOWLER.

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THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

•*Executive Committee.*